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Editorial

Progress in Sarcoidosis

ALTHOUGH it may be something of an overstatement to speak of progress in sarcoidosis when the central problems of etiology, histopathology and therapy remain in an unsettled state, the last decade has certainly seen an accumulation of data which have clarified some aspects of this puzzling condition; to that extent at least, there has been progress.

The breach is still wide between those who believe that sarcoidosis is a disease entity unto itself, of as yet undiscovered etiology, and those who believe that sarcoidosis most often represents an exceptional phase of tuberculosis. Most American and Scandinavian observers favor a non-tuberculous etiology and regard the occasional occurrence of tuberculosis in patients with sarcoidosis as a complication akin to tuberculosis superimposed upon silicosis or bronchogenic carcinoma. On the other hand, many students of the disease in Great Britain and on the Continent lean toward linking most cases of sarcoidosis to the tubercle bacillus. For more than thirty years this latter school has maintained that sarcoidosis is a special form of tuberculosis occurring in persons with unusual humoral and tissue responses to the tubercle bacillus. Briefly stated, this view suggests that in patients with sarcoidosis there may be an enhanced capacity for destroying tubercle bacilli in their tissues; this accounts for the inability to identify the bacilli in sarcoid tubercles. By destroying bacilli in the tissues, it is argued, large amounts of tuberculin are released into the blood stream. Presumably, this calls forth an immunologic response in the form of tuberculin-neutralizing substances, which accounts for the relative tuberculin insensitivity and, supposedly, for the unusual hyperimmune state characterized as "positive anergy."

The concept of positive anergy in sarcoidosis has fallen somewhat into disfavor in recent years. Two reasons may be mentioned. First, it has been shown that patients with sarcoidosis do not have tuberculin-neutralizing substances in their serums more often or in any greater amount than do normal subjects [*1*]. Second, it has been demonstrated that BCG organisms remain alive at the vaccination sites for just as long a period in sarcoidosis patients as in normal susceptible control subjects [*2,3*].

Still, workers favoring the tuberculous etiology of sarcoidosis point to the relative frequency with which the tubercle bacillus eventually turns up in patients with sarcoidosis [*4*]. They are impressed, too, with the striking clinical similarity between sarcoidosis and occasionally encountered cases of indolent, tuberculin-negative tuberculosis. They advance the intriguing idea that these cases form a bridge between sarcoidosis and frank caseous tuberculosis. They also cite the fact that these indolent forms of tuberculosis, like sarcoidosis, often prove quite unresponsive to the usually effective antituberculosis drugs. Finally, they suggest the term "tuberculous sarcoidosis" for most cases in the idiopathic group to distinguish them from "beryllium sarcoidosis," "histoplasma sarcoidosis" and the like [*5*].

The failure thus far to isolate an etiologic

[1] MAGNUSSON, B. The effect of sarcoidosis sera on the tuberculin response. *Acta dermat.-venereol.* (Suppl.), 35: 1–138, 1956.

[2] ROSTENBERG, A., JR. et al. Experimental studies on sarcoidosis. *Arch. Dermat. & Syph.*, 67: 306, 1953.

[3] FORGACS, P. et al. The BCG lesion in sarcoidosis. *Lancet*, 272: 188, 1957.

[4] SCADDING, J. G. Insensitivity to tuberculin in pulmonary tuberculosis. *Tubercle*, 37: 371, 1956.

[5] Editorial. Sarcoidosis. *Lancet*, 271: 1339, 1956.

agent in sarcoidosis and to transmit the disease to an experimental animal has forced an indirect approach to the problem of etiology. It may be helpful now to examine the question of etiology in the light of some recent data.

Negative tuberculin reactions in sarcoidosis do not necessarily imply the absence of prior tuberculous infection. Such insensitivity is reported for about two-thirds of adult patients with sarcoidosis but it is, for the most part, a result of suppression of a previously existing tuberculin sensitivity. This has been suggested by two sets of observations. First, a number of patients with sarcoidosis are known to have had positive tuberculin reactions before the onset of sarcoidosis. Their sensitivity has been found to wane and disappear when clinical sarcoidosis appears, and many are found to become tuberculin-sensitive again when the sarcoidosis regresses [*6*]. Second, evidence of previous tuberculous infection has been demonstrated by intracutaneous testing of patients with sarcoidosis with tuberculin suspended in liquid paraffin, so-called "depot-tuberculin," instead of the conventional aqueous suspension. In oily menstruum the tuberculin yields almost as high a frequency of positive reactions among patients with sarcoidosis as it does among control subjects of the normal population [*7,8*]. These two sets of findings suggest that most patients with sarcoidosis are actually tuberculin-sensitive but they cannot fix aqueous tuberculin at the injection site long enough to elicit the positive reaction. Lack of fixation is probably not the only factor. There may be a defect in the ability of patients with sarcoidosis to marshal the quantity or quality of white blood cells which are thought to transport to the skin the antibodies responsible for the delayed tuberculin-type reaction [*9*].

Despite the tuberculin insensitivity, neither complement fixation nor agglutinin antibody formation is depressed in sarcoidosis [*10–12*]. Moreover, unresponsiveness to tuberculin in sarcoidosis appears to be non-specific since it extends to other cutaneous antigens of the delayed tuberculin-type reaction; that is, trichophytin, oidiomycin, histoplasmin, mumps virus and pertussis agglutinogen [*10,11,13*].

It is of interest in this connection that patients with Hodgkin's disease display a parallel feebleness of response to tuberculin and some of the other antigens cited [*14*]. This suggests that perhaps the involvement of the reticuloendothelial system, which is common to both Hodgkin's disease and sarcoidosis, depresses the cutaneous reactivity to antigens giving delayed tuberculin-type reaction. To a degree, the common behavior of the two diseases in this respect tends to favor a non-tuberculous etiology of sarcoidosis.

On the other hand, some support for a tuberculous etiology of sarcoidosis has recently been afforded by an ingenious approach through search for bacterial residues in sarcoid tissues. Netherscott and Strawbridge [*15*] subjected hydrolysates of sarcoid tissues from four patients to an analysis aimed at detecting specific amino acid and lipid fractions of tubercle bacilli within the tissues. By means of chromatophoresis they isolated substantial amounts of diaminopimelic acid (DAP), a component of tubercle bacilli. By infra-red spectrophotometry they also identified an acid-fast fatty acid with a spectrum like that of mycolic acid, another component of the tubercle bacillus. The investigators concluded from these findings that at some time in the past the tissues contained live tubercle bacilli which were responsible for the sarcoid changes. Shortly after publication of these findings, however, a number of objections were raised

[6] Nitter, L. Changes in the chest roentgenogram in Boeck's sarcoid of the lungs. *Acta Radiol.* (Suppl.), 105: 1–202, 1953.

[7] Seeberg, G. Tuberculin sensitivity in lymphogranulomatosis benigna. *Acta dermat.-venereol.*, 31: 426, 1951.

[8] James, D. G. and Pepys, J. Tuberculin in aqueous and oily solutions: skin test reactions in normal subjects and in patients with sarcoidosis. *Lancet*, 270: 602, 1956.

[9] Pepys, J. The relationship of non-specific and specific factors in the tuberculin reaction. *Am. Rev. Tuberc.*, 71: 49, 1955.

[10] Sones, M. and Israel, H. L. Altered immunologic reactions in sarcoidosis. *Ann. Int. Med.*, 40: 260, 1954.

[11] Quinn, E. L., Bunch, D. C. and Yagle, E. M. The mumps skin test and complement fixation test as a diagnostic aid in sarcoidosis. *J. Invest. Dermat.*, 24: 595, 1955.

[12] Sands, J. H., Palmer, P. P., Mayock, R. L. and Creger, W. P. Evidence for serologic hyper-reactivity in sarcoidosis. *Am. J. Med.*, 19: 401, 1955.

[13] Friou, G. J. A study of the cutaneous reactions to oidiomycin, trichophytin and mumps skin test antigens in patients with sarcoidosis. *Yale J. Biol. & Med.*, 24: 533, 1952.

[14] Schier, W. W., Roth, A., Ostroff, G. and Schrift, M. H. Hodgkin's disease and immunity. *Am. J. M.*, 20: 94, 1956.

[15] Netherscott, S. E. and Strawbridge, W. G. Identification of bacterial residues in sarcoid lesions. *Lancet*, 271: 1132, 1956.

to this interpretation. It was shown that DAP is a component of a host of unrelated microorganisms and that it can also be found in normal lymph nodes [*16–18*]. It was also maintained that the methods used for identifying mycolic acid were faulty and that some normal tissues contain lipids of almost identical structure and could not readily be differentiated from mycolic acid [*18,19*]. The problem requires more investigation and, in the meantime, the matter must remain *sub judice*.

A new field of progress in sarcoidosis is that of epidemiology. Michael [*20*] and later Cummings [*21*] made surveys of patients with sarcoidosis in the United States Army and among Veterans Administration patients. These surveys included 350 and 1,194 cases of sarcoidosis, respectively, mostly among young men. An unusual geographic distribution of the disease in the United States was unfolded. The principal "endemic" areas were located in the southeastern states, with some small pockets in New England and the Midwest. Michael noted that sarcoidosis was predominantly a disease of rural areas. He considered this to be an argument against tuberculosis as a cause of sarcoidosis since tuberculosis in the United States is essentially an urban disease. Unexplained was the high incidence of sarcoidosis among Negroes. Whereas Michael noted some correlation between the frequency of sarcoidosis and some beryllium-containing soils, Cummings was impressed with the high incidence of the disease in the forested areas of the United States.

As can be seen, we are not much closer to discovering the cause or, as some workers would have it, the multiple causes of sarcoidosis than we were a decade ago. The fact remains, however, that even those physicians who feel strongly about the tuberculous etiology of sarcoidosis behave as if the disease were not tuberculosis. Given a young asymptomatic patient with bilateral, symmetrically enlarged hilar nodes, a negative tuberculin reaction and a prescalene lymph node biopsy specimen which shows epithelioid-cell tubercles, the physician feels no urgency to treat the patient with antituberculosis drugs to prevent spread of the process; he does not insist on prompt examination of all familial and household contacts for evidence of a source case or a secondary case of tuberculosis; nor does he inform the health authorities that a public health menace may exist. In short, he does none of the things he ordinarily might do on discovering a new case of tuberculosis.

Admittedly, the bilateral hilar node syndrome is not representative of the entire gamut of sarcoidosis. The problem is more complex when only the lungs appear to be involved. But in such instances every attempt is made to differentiate pulmonary sarcoidosis from pulmonary tuberculosis even if the physician believes that one disease is but a phase of the other. The need for him to do this is especially great in certain cases in which treatment with steroids might prove extremely helpful, as in sarcoidosis patients with acute pulmonary insufficiency, whereas such treatment might be harmful in a patient with tuberculosis.

The relationship to tuberculosis should become clearer as the incidence of tuberculosis continues to decline. This should eventually lead to a decrease in the incidence of sarcoidosis if the two conditions are related. The tubercle bacilli isolated from patients with sarcoidosis have always been found to be of the expected virulence for guinea pigs; clearly, an unusual form of acid-fast organisms is not the explanation of sarcoidosis.

Teilum's [*22*] theory of allergic hyperglobulinosis and Refvem's [*23*] speculation of the relationship of phospholipids to sarcoidosis have also aroused considerable interest.

None of the foregoing data in any degree represent proof of the tuberculous or nontuberculous etiology of sarcoidosis, nor do any of the investigators holding one or another view

[16] Work, E. Correspondence. Identification of bacterial residues in sarcoid lesions. *Lancet*, 271: 1310, 1956.

[17] Cummins, C. S. and Harris, H. Correspondence. Identification of bacterial residues in sarcoid lesions. *Lancet*, 272: 106, 1957.

[18] Consden, R. Correspondence. Identification of bacterial residues in sarcoid lesions. *Lancet*, 272: 106, 1957.

[19] Berg, J. W. Correspondence. Identification of bacterial residues in sarcoid lesions. *Lancet*, 272: 272, 1957.

[20] Michael, M., Cole, R. M., Beeson, P. B. and Olson, B. J. Sarcoidosis. Preliminary report on study of 350 cases with special reference to epidemiology. *Am. Rev. Tuberc.*, 62: 403, 1950.

[21] Cummings, M. M. Concepts of epidemiology of sarcoidosis. *Postgrad. Med.*, 19: 437, 1956.

[22] Teilum, G. Allergic hyperglobulinosis and hyalinosis (paramyloidosis) in the reticuloendothelial system in Boeck's sarcoid and other conditions. *Am. J. Path.*, 24: 389, 1948.

[23] Refvem, O. The pathogenesis of Boeck's disease. *Acta med. Scandinav.* (Suppl.), 294: 1–146, 1954.

on the matter claim that the etiology is known. The various views cited do, however, reflect trends of present-day thinking on this crucial question.

An important advance in the diagnosis of sarcoidosis has come from some of the newer methods for obtaining tissue biopsies for confirming the diagnosis, and from a realization that many more organs contain the tell-tale epithelioid-cell tubercles in the early phases of the disease than was previously suspected. To the commonly employed peripheral lymph node and cutaneous biopsies have been added prescalene lymph node biopsy, liver aspiration, open lung biopsy, random muscle biopsy, bronchoscopic and nasopharyngeal biopsies. By the addition of chemical and mycologic studies of tissues showing epithelioid-cell tubercles, granulomas caused by beryllium and histoplasmosis are being identified more easily. Difficulties still remain in distinguishing those tubercles of sarcoidosis showing fibrinoid change or slight necrosis from tubercles with areas of true caseation, such as occur in frank tuberculosis and other conditions. In spite of special tissue and bacterial stains, the problem may prove vexing [*24*].

Interestingly enough, when tuberculosis is associated with sarcoidosis the caseous lesions are usually found in the organs which ordinarily are affected by tuberculosis—lungs, lymph nodes, liver, spleen. Caseation is not found in the tubercles of organs where tuberculosis is rare—the salivary glands, muscles, eyes. It may be reasoned that if sarcoidosis is a non-caseous form of tuberculosis, caseous transformation should be encountered in all organs in which sarcoidosis tubercles are present—in the parotids, eyes and muscles as well as in the lung and lymph nodes. Absence of caseation in salivary glands, muscles and eyes lends some weight to the contention that when tuberculosis occurs it is a complication of sarcoidosis and not a different phase of the same disease.

A step forward in the diagnosis of sarcoidosis has come with the introduction of an intracutaneous test by Nickerson [*25*] in 1939 and, independently, by Kveim [*26*] in 1941. These workers showed that when a crude saline suspension of ground sarcoid lymph nodes or spleen is injected intracutaneously into patients with sarcoidosis a small papule often appears which grows slowly and may persist for months. Excision of the papule after four to eight weeks usually discloses a microscopic pattern of organized tuberculoid granlomas similar to that seen in spontaneously-occurring sarcoidosis lesions. On the other hand, no significant papule appears in normal subjects or in patients with other diseases; if a papule does appear it shows only non-specific or foreign body inflammatory lesions which do not have the architecture of a positive Nickerson-Kveim reaction.

Since these initial reports of Nickerson and Kveim, a number of reports have appeared which, except for a single recent dissent, have confirmed the usefulness of the Nickerson-Kveim test as an adjunctive diagnostic tool in sarcoidosis. Where standardized testing suspensions are available, the intradermal test has come to be considered a necessary part of the diagnostic procedure. The test cannot, however, be used as a substitute for biopsy of an involved organ, which is still the primary means of support of the diagnosis of sarcoidosis. Most workers find the test especially helpful in situations in which no tissue confirmation of the diagnosis has come to hand, either because organ biopsy material is not informative or biopsy for some reason has not been undertaken.

Even when organ biopsy material shows the characteristic picture of epithelioid-cell tubercles without caseation, a positive Nickerson-Kveim test can still be of diagnostic import whenever the clinical findings are not typical enough to help separate sarcoidosis from other granulomatous conditions. As stated, this distinction must be made if proper therapy is to be applied.

With increasing experience more has been learned about the behavior of the testing suspensions and about what constitutes a positive Nickerson-Kveim reaction. First, sarcoid tissue suspensions are the only satisfactorily specific diagnostic agents for the intradermal test. Heat-killed tubercle bacilli, BCG and tuberculin do not regularly produce dermal granulomas of tuberculoid architecture. Moreover,

[24] ZETTERGREN, L. Lymphogranulomatosis benigna: a clinical and histo-pathological study of its relation to tuberculosis. *Acta Soc. Med. Upsal.* (Suppl.), 5: 1–180, 1954.

[25] NICKERSON, D. A. Cited by Appel, B. Sarcoid. *Arch. Dermat. & Syph.*, 43: 172, 1941.

[26] KVEIM, A. En ny og spesifik kutan-reackjon ved Boeck's sarcoid. *Nord. med.*, 9: 169, 1941.

when these agents produce dermal granulomas they do so as frequently in control subjects as in patients with sarcoidosis. Second, quartz, diamond dust, talc, cotton, india ink, normal lymph node and normal splenic tissue and a host of other substances have been injected intradermally in patients with sarcoidosis without producing changes other than non-specific inflammation or foreign-body granulomas. Patients with sarcoidosis are no more prone to show these changes than are other subjects, indicating that there is no underlying "sarcoid diathesis" to explain the positive Nickerson-Kveim reactions among patients with the disease [*23*]. Nor do patients with sarcoidosis give histories indicating a greater frequency of the common allergic disorders.

Not all sarcoid tissue, even that exhibiting the classic microscopic pattern, will yield potent and specific testing suspensions. Thus in one series [*27*] five of fifteen suspensions were inert on bio-assay and two more had to be discarded when they began to provoke non-specific inflammatory papules in all classes of patients tested. Nelson [*28, 29*] found three of ten suspensions of sarcoidosis tissue inert and he discarded two others when they deteriorated and produced non-specific papules. Putkonen [*30*] prepared and evaluated twenty sarcoid tissue suspensions. He found seven satisfactory but had to discard the remaining thirteen because they were either too weak or too irritating. As can be seen, one cannot predict which sarcoid tissue suspension will prove active and specific. Each batch must be assessed in sarcoidosis patients of known responsiveness and the bio-assay is best repeated periodically as a check against possible deterioration. Some active suspensions have remained unaltered over a seven-year period.

The occasional occurrence of non-specific inflammatory reactions and foreign body granulomas after intradermal injections with certain sarcoid tissue suspensions is not surprising when the crude nature of the testing suspensions and the tissues which are usually employed in preparing them are considered. The best suspensions are made from sarcoid lymph nodes and spleen. Since these organs are, among other things, organs of filtration in the body, they may contain bacteria including tubercle bacilli or fungi. Although every precaution is taken to detect the presence of these microorganisms before preparing suspensions, viral, bacterial and fungal residues as well as exogenous and endogenous foreign material and other débris cannot, at present, be eliminated during the processing. In fact, as Ehrlich [*27*] has pointed out, lint fibres and other foreign materials can easily be accidently introduced into the suspensions unless special precautions are taken. Polarized light is helpful in detecting these fibres when examining the biopsied test sites microscopically. It is these contaminants which cause the troublesome non-specific dermal reactions that make biopsy of every papule an obligatory procedure in the Nickerson-Kveim test. If the active fraction in the testing suspensions is ever identified many of these non-specific reactions probably could be eliminated and the need for biopsy of the test site might vanish. In any event, in spite of the difficulties described, small batches of testing suspensions are relatively easy to prepare and use, and their diagnostic worth more than compensates for the tedium attached to preparing and standardizing them.

The literature shows that almost all investigators report a favorable experience with the Nickerson-Kveim test and consider it a diagnostic measure of high specificity in sarcoidosis. In all, more than 560 patients (including some unpublished personal observations) with sarcoidosis, confirmed by biopsy, have received one or more Nickerson-Kveim intradermal tests. Most of the results reported recently are based on a microscopic reading of the excised test site [*27–29,31–35*]. In

[27] Siltzbach, L. E. and Ehrlich, J. C. The Nickerson-Kveim reaction in sarcoidosis. *Am. J. Med.*, 16: 790, 1954.

[28] Nelson, C. T. Kveim reaction in sarcoidosis. *Arch. Dermat. & Syph.*, 60: 377, 1949.

[29] Nelson, C. T. and Schwimmer, B. The specificity of the Kveim reaction. *J. Invest. Dermat.*, 28: 55, 1957.

[30] Putkonen, T. Ueber die Intrakutanreaktion von Kveim (KvR) bie Lymphogranulomatosis benigna. *Acta dermat.-venereol.* (Suppl. 10), 23: 1–194, 1943.

[31] Rogers, F. J. and Haserick, J. R. Sarcoidosis and the Kveim reaction. *J. Invest. Dermat.*, 23: 389, 1954.

[32] James, D. G. and Thomson, A. D. The Kveim test in sarcoidosis. *Quart. J. Med.*, 24: 49, 1955.

[33] Bloch, R. G. Personal communication.

[34] James, D. G. Diagnosis and treatment of sarcoidosis. *Brit. M. J.*, 2: 900, 1956.

[35] Reid, J. D. Use of Kveim test in diagnosis of sarcoidosis. *New Zealand M. J.*, 55: 275, 1956.

[36] Danbolt, N. On the skin test with sarcoid tissue suspension (Kveim's reaction). *Acta dermat.-venereol.*, 31: 184, 1951.

some studies not all papules were biopsied [*6,23,26,30,36*].

The incidence of positive reactions reported among the group with sarcoidosis confirmed by biopsy ranged between 65 and 92 per cent. Thus a high proportion of patients respond to the test and satisfactory sarcoid-tissue testing suspensions should give a high incidence of positive reactions in patients with sarcoidosis.

As "control" material, the cumulative series provides data on 585 patients with diseases other than sarcoidosis, or with no demonstrable illness. This control group shows only eleven patients with positive Nickerson-Kveim reactions, a "false-positive" reaction frequency of only 2 per cent. Many patients with active tuberculosis were among those tested in the control group. These numbered 218 patients and among them three false-positive reactions were reported, an incidence of about 1.5 per cent. These are satisfactorily low rates of false-positive reactions for a biologic test.

Sones and Israel [*37,38*] recently reported unfavorable experiences with the Nickerson-Kveim reaction. For their studies they had available a batch of testing suspensions which they prepared from the lymph nodes of a patient with biopsy-confirmed sarcoidosis. With this material, processed in the usual manner, they found positive Nickerson-Kveim reactions in only 21 per cent of tests performed on twenty-eight patients with sarcoidosis. Measured against the 65 to 92 per cent responses obtained with similar patients by other investigators, their testing suspensions showed diminished potency. Among their control subjects were thirty-three patients with active tuberculosis. These patients showed false positive responses amounting to 42 per cent. A few patients with diseases other than tuberculosis also gave false-positive reactions.

These unsatisfactory results suggest that the lymph nodes employed by Sones and Israel were not a suitable source of testing material. Using the criteria generally adopted for standardizing Nickerson-Kveim suspensions by bioassay, their testing material perhaps was too weak and too non-specific to be adequate for use as a diagnostic agent in sarcoidosis. This interpretation seems to be reinforced by Sones and Israel's finding that their tuberculosis patients no longer gave any false-positive reactions when the testing suspensions were filtered. Yet the filtered suspensions retained the capacity to evoke positive Nickerson-Kveim reactions as frequently as when in the unfiltered state. Hence it would appear that some contaminants responsible for the confusing intradermal reactions in their series were adherent to the grosser particles in the unfiltered suspensions. A few patients with tuberculosis were also tested with sarcoid tissue suspensions borrowed from other workers, but no false-positive results were obtained.

There is great need for a constant supply of standardized testing suspensions and for clearer criteria in the microscopic examination of the test sites. Even with standardized suspensions borderline and equivocal reactions crop up now and again.

The exact mechanism responsible for the positive Nickerson-Kveim reaction in sarcoidosis is not understood, nor does the test throw much light on the etiology of the condition.

With respect to corticotrophin and corticosteroid therapy for sarcoidosis, almost all would agree that their introduction has been, in many instances, a great boon. These agents promptly suppress many of the acute organ-threatening and sometimes even life-threatening effects of the disease, and indeed offer the only reliable means of tiding a patient over such dangerous episodes. As in other chronic and recurrent diseases, these drugs are not curative and their discontinuation is often followed by prompt relapse. Prednisone and prednisolone have simplified the management of steroid therapy.

The danger of reactivation of tuberculosis in treated patients has fortunately proved to be a problem of relatively insignificant proportions.

At the present time the steroids are best used in the following situations: acute miliary dissemination in the lungs, with alveolar-capillary block syndrome; progressive lung involvement with significant symptoms; late fibrotic scarring with disabling dyspnea (in this instance as symptomatic therapy) [*39,40*]. Ocular, central nervous system and direct cardiac involvement,

[37] Sones, M., Israel, H. L., Krain, R. and Beerman, H. Kveim test in sarcoidosis and tuberculosis. *J. Invest. Dermat.*, 24: 353, 1955.

[38] Israel, H. G. and Sones, M. The diagnosis of sarcoidosis with special reference to the Kveim reaction. *Ann. Int. Med.*, 43: 1269, 1955.

[39] Siltzbach, L. E. Effects of cortisone in sarcoidosis; a study of thirteen patients. *Am. J. Med.*, 12: 139, 1952.

[40] Siltzbach, L. E. Pulmonary sarcoidosis. *Am. J. Surg.*, 89: 556, 1955.

also splenic involvement with hematologic disorders, are advantageously so treated. Finally, disfiguring cutaneous lesions, very large superficial lymph nodes, salivary gland involvement, fever, marked weight loss, muscle atrophy and persistent hypercalcemia with renal damage—all these have been improved with steroid therapy. Courses usually last two to six months; in some patients therapy must be maintained indefinitely.

It is now more than eighty years since Hutchinson described his first case of sarcoidosis and more than fifty years since Boeck made his basic contributions. For most investigators, delving into sarcoidosis has been like working in a dark room. But recently some light has been seeping in as if through a crack in the door. When that door will finally be fully opened none can even vaguely guess.

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Clinical Studies

Acute Hemorrhagic Cystitis*

An Infection Associated with Pleuropneumonia-like Organisms and Related to Urethritis and Prostatitis

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ACUTE abacterial pyuria has been presumed to be an infection due to an unidentified organism [*1–6*]. It is characterized by pyuria, hematuria, frequency and urgency, fever, superpubic and perineal pain and severe hemorrhagic inflammation of the bladder with membranous sloughs. It does not respond to sulfonamides or penicillin but does respond to arsenicals to some extent.

The observations presented in this paper suggest that such acute hemorrhagic cystitis (a term we prefer to abacterial pyuria) is caused by pleuropneumonia-like organisms (PPLO). These organisms are often present in inflammatory conditions of the urethra and can apparently extend from the urethra to the bladder. There is some evidence that they can also produce a generalized infection with arthritis and conjunctivitis. These organisms are usually sensitive to streptomycin and the tetracyclines although not to sulfonamides and penicillin.

SUBJECTS AND METHODS OF STUDY

The patients and control subjects who were studied fall into three main groups as shown at the top of page 849.

The clinical picture of acute hemorrhagic cystitis is drawn from the fifteen cases included in groups B and C. These were all patients in whom the diagnosis was substantiated by cystoscopy and in whom positive cultures for PPLO were found. Most of them (the eleven Navy subjects) were patients who appeared at a large Naval Hospital with unexplained genitourinary tract infections, usually unresponsive to sulfonamides and penicillin.

In addition to the clinical description of acute hemorrhagic cystitis, a composite description is presented of the findings in all fifty-seven Navy patients presenting with unexplained genitourinary tract infections with positive cultures for PPLO. This includes the eleven Navy patients with acute hemorrhagic cystitis substantiated by cystoscopy. Such an over-all description is of interest insofar as it reflects the extent and variety of findings in patients with PPLO in the genitourinary tract, who have been shown to have none of the ordinary genitourinary tract pathogens. It is more difficult to draw conclusions as to the pathogenicity of PPLO from this entire group, however, because of the extent of the ordinary flora in the lower genitourinary tract.

Control Series. To interpret the significance of positive cultures for PPLO, cultures were taken from ninety-eight men presumed to be without genitourinary complaints. Two groups were studied: the first group (patient controls) consisted of fifty-one men who were hospitalized for other than genitourinary tract illnesses, and the second group (separatees) consisted of forty-seven enlisted men who were in the process of separation from the service. These were included in the 108 control subjects reported earlier [*7*].

Culturing Technic. In the first group of control subjects a single urethral loop only was cul-

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- Navy patients with unexplained genitourinary infections (88)
  - (A) PPLO-positive (57) — (B)
    - Patients with cystoscopic evidence of acute hemorrhagic cystitis (11)
    - Patients with various sites of genitourinary tract infection including one with probable cystitis but in whom cystoscopy was not performed (46)
  - PPLO-negative (31)
    - Patients with cystoscopic evidence of cystitis (3)
    - Patients with various sites of genitourinary tract infections including three with probable cystitis but in whom cystoscopies were not performed (28)
- Other PPLO-positive patients (9) — (C)
  - Patients with cystoscopic evidence of acute hemorrhagic cystitis (Cases A–D) (4)
  - Patients with various sites and findings of upper urinary tract infections (Cases E–I) (5)
- Navy controls (98)
  - Navy patient controls: Hospitalized patients not presenting complaints referable to genitourinary tract (51)
  - Separatees: Men in the process of being separated from the Naval Service (47)

tured. Thereafter attempts were made to culture separately the urethra, bladder urine and prostatic fluid. Such a separation can only be approximate. Catheters inserted into the bladder may carry urethral and prostatic fluid organisms with them; a "clean" specimen (a second glass aliquot) may wash out urethral organisms. As an approximation, specimens were obtained as follows: Specimen A: from a bacterial loop inserted about 1 inch into the anterior urethra; Specimen B: from prostatic fluid expressed by massage or (if no frank fluid) from a second urethral loop after massage, following the passing of an initial portion of urine; Specimen C: the final portion of urine. Under these circumstances a positive result in C may arise from the bladder or prostate if B is also positive. Alternately, the first urine could have been passed after specimen A, but in that case a positive result in B could have been due to either urethral or prostatic disease if A were also positive. In the early part of the study two specimens only were obtained: specimen D: urine after prostatic massage; specimen E: urine before prostatic massage.

With these limitations it was not possible to identify the origin of organisms or leukocytes with certainty. However, urethritis was diagnosed when a urethral discharge was unaccompanied by pus in the prostatic fluid; prostatitis and urethritis was diagnosed when leukocytes were found in the prostatic fluid (an aliquot of urine having previously been passed) (specimen B); and cystitis was diagnosed only after cystoscopy. Epididymitis was not diagnosed unless there was swelling as well as subjective discomfort.

Urethral loop cultures were directly streaked on boiled blood ascitic agar; prostatic fluid was allowed to drop on agar plates and then streaked; urine samples were centrifuged for ten minutes at 2,000 r.p.m. and the sediment was then streaked on the agar plates. A culture of B. prodigiosus was planted on the Petri dish cover to produce a strictly anaerobic culture, and the rim of the Petri dish was sealed with paraffin. After forty-eight hours' incubation at 37 degrees the surface of the agar was inspected with a hand lens for the minute transparent colonies. A section of the agar was then cut out, stained with methylene blue-Azure II, following the technic formerly described [*18*]. Under high-power magnification the typical colonies could be readily identified [*8,9*].

In reviewing the history and physical examination of patients and control subjects, all genitourinary findings were noted including any incident at any time relating to the genitourinary tract. The prostate was described in terms of size, hardness, irregularity, tenderness and change during massage.

Effectiveness of Streptomycin Therapy. In evaluating the effectiveness of a drug in curing a disease, an experimental design must allow a comparison of the duration of disease in treated patients with that in untreated patients. This is usually accomplished by treating alternate patients.

Another method has been used in this study. With this alternate experimental design, no patient is treated until he has been sick so long that a spontaneous recovery during a relatively brief period of therapy would be unlikely. How unlikely this would be can be approximated by estimating the average duration of illness which could be expected after beginning therapy. These values can then be compared with the actual durations when specific treatment is given. For this calculation there is needed a knowledge of the distribution of total durations of the disease. Such a distribution has been calculated for the present material by an indirect method to be reported elsewhere [*28*].

TABLE I
THE PRINCIPAL CLINICAL FINDINGS IN FIFTEEN CASES OF ACUTE HEMORRHAGIC CYSTITIS

Onset:	
Urethritis	6
Cystitis	8
Both	1
Duration: Average 1 mo.	
First episode	10
Second episode	5
Previous episodes: 3 mo. to 3 yr.	
Hematuria:	
At onset	5
4 days to 6 wk. later	5
Frequency	15
Urgency	15
Pain:	
Suprapubic	7
Perineal	3
Conjunctivitis	3
Arthritis	2
Follicular rash	1
Epididymitis	1
Prostate firm or nodular	8
Cystoscopy:	
Membranous sloughs	10
Marked injection	15
Petechiae	1
Scarlatiniform	1
Ureteral orifice edema	4
Ulceration	3

RESULTS

Clinical Findings in Acute Hemorrhagic Cystitis. The presenting symptoms in the fifteen patients with cystitis proved by cystoscopy (groups B and C) are shown in Table I. The cystitis appeared acute, preceded in some by an indolent urethritis, and was characterized by marked frequency, urgency, hematuria (occasionally only terminal) and suprapubic or perineal pain. This occasionally radiated to the penis or testicles and sometimes required opiates for relief. A few patients became acutely ill with fever, a leukocytosis of 12,000 to 18,000 and marked malaise. Without treatment these episodes in some patients persisted for prolonged periods, with partial remissions and exacerbations and a loss of weight. Occasionally there was hydronephrosis subsequent to the intense edema of ureteral orifices and it was accompanied by costovertebral angle tenderness. Acute epididymitis developed in one patient, conjunctivitis in three patients and arthritis in two. On treatment with streptomycin remarkable improvement was often noted within twenty-four hours, with clearing of symptoms by approximately the fifth day.

Interesting Patients without Cystoscopy. (Appendix, Other Cases, E-I). In two of these patients marked hydronephrosis developed as a result of obstruction at the ureteral orifices. Two patients gave evidence of pyelonephritis and one of these had calcinosis of the kidney. Two patients had both joint and eye involvement. One of these had an acute exacerbation of conjunctivitis on the day following nephrectomy. One patient had scaling, bulbous lesions of the soles consistent with keratodermia blenorrhagicum. A remarkable case of cystitis, arthritis and conjunctivitis with PPLO in the urine has been reported by Warthin [*10*]. This patient eventually succumbed to generalized amyloidosis [*11*].

Clinical Findings in Patients with Genitourinary Complaints and Positive Cultures for PPLO. This information includes all fifty-seven patients from the Navy Series with urethritis, prostatitis and/or cystitis (group A).

Seasonal Incidence. The percentage of positive cultures for PPLO among patients with unexplained genitourinary complaints was highest in the summer months (88 per cent of patients studied in one month), as was the total number of unexplained genitourinary infections.

Age Incidence. The average of 22.3 years compared with an average age of all hospitalized patients of 27.1 years.

Source of Infection. Most patients with positive cultures had had recent venereal exposure. In twenty cases in which a comparatively isolated exposure could be identified the average latent period after exposure was nineteen days. (Compared with 15.2 days, Ambrose and Taylor [*12*]). Symptoms developed in eight men within ten days.

Symptoms. Among the fifty-seven patients with positive cultures for PPLO, fifty-one had a discharge, thirty-one burning sensation, twenty-one urinary frequency and eleven hematuria. Burning and frequency commonly appeared with the initial discharge. Hematuria was usually terminal although occasionally the urine was grossly bloody. In one patient with urethral polyps it had persisted for months without other symptoms.

Another occasional symptom was an itching sensation in the anterior urethra. Sometimes there was sharp and severe penile pain. A few patients had costovertebral angle pain but no other evidence for upper genitourinary tract disease was obtained in these patients.

Physical Findings. The cystoscopic findings were rather characteristic. In cases of urethritis there was infection, occasionally petechial, easy bleeding, and sometimes a superficial whitish membrane which stripped away revealing puntate bleeding points. This was most common in the posterior urethra, especially over the vera montanum.

The prostate was abnormal to palpation almost without exception, characteristically enlarged, firm, nodular and tender. In a few instances the prostate was boggy or shrunken. Massage frequently resulted in temporary improvement in the firmness and nodularity of the gland.

The prostatic fluid was often normal despite the grossly abnormal gland. However, in the course of remission both the prostate and its secretion tended to revert to normal.

Penile lesions were observed in twelve patients. These were usually 1–2 mm. lesions in the following forms: multiple coronal papules, 3; single coronal papules, 1; single papules on the shaft, 1; vesicular papules, 2; single macules, 2; single ulcer, 2; and in one patient a very reddened urethral meatus. These were present only during the acute illness, lasting from three days to three weeks, except that in one patient (No. 14) multiple coronal papules persisted for at least two years and their appearance antedated the urethritis by some five months.

Joint symptoms as a part of the acute illness were present in fourteen cases but there were objective findings in only six of these. Of these six patients, four had the findings of acute infectious arthritis. In patient No. 1 there was involvement of the right knee and ankle, in patient No. 6 the left wrist only, in patient No. 24 the left knee and right great toe, and in patient No. 42 the ankles' knees and feet, associated with erythema nodosum. In two of these four persistent chronic arthritis developed and lasted for many months.

A fifth patient had a transient swelling in the left ankle, and in the sixth patient a symmetrically progressive reddening and swelling of the terminal interphalangeal joints of fingers and toes developed and lasted for approximately seven months. These joints were slightly tender, and the adjacent nails were pitted. They resembled psoriatic nails but there was no psoriasis. This was the same patient (No. 14) who had a persistent penile eruption for two years. Both the eruption and the arthritis showed no improvement during the period of observation.

The eight patients who had symptoms without objective evidence of arthritis had more chronic complaints, restricted to the low back in four, the low back and shoulders in one, and generalized in three.

Involvement of the eyes was present in eight patients as a mild chronic conjunctivitis lasting from three weeks to six months. Injection was always more prominent then exudation. Excessive tearing was the only symptom in one of these patients. Another had episodes of conjunctival injection lasting one day, with involvement of the other eye on the following day. Such episodes could be precipitated by prostatic massage. This patient (No. 2) was the only one with both objective eye and joint findings. Five others among the thirty treated patients had involvement of both joint and eye symptomatically but the joints were not abnormal to inspection.

Skin manifestations in five patients consisted of erythema nodosum in one, herpes simplex of the lip on the eleventh day of a combined urethritis and arthritis in another patient, scaling colorless papules of the dorsum of the hands in a third, generalized papular eruption associated with plantar vesicles in a fourth, and a generalized folliculitis in a fifth. These were all part of the acute illness.

Constitutional evidences of disease were common although most patients felt generally well. Malaise, weight loss and fatigue were present in roughly a fourth of the cases. Significant fever was present in only four patients, two with acute arthritis and two with acute hemorrhagic cystitis. In the latter group one patient (No. 25) ran a spiking fever to 104°F. for many weeks and

TABLE II

CULTURES FROM ELEVEN PATIENTS WITH CYSTITIS AS ESTABLISHED BY CYSTOSCOPY

Case No.	Source of Cultures*	Results of Cultures															
24	A	+++	...	0	...	0	...	++++	...	0	Few SA, D	++	...	0			
	B	+++	...	0	...	0	...	++++	Few SA, D	0	Few SA, D	0		0			
	C	+++	...	0	...	0	Few SA, D	++++	...	0	...	0		0			
		(15)†		(3)		(85)		(133)		(146)		(205)		(213)			
7	A	0	...	+++	Ab‡ S, D	0	Few C, St	0	Few SA, St	0	Ab St, D Mod‡ SA	.....		.....			
	B	0	...	+++	Few St	0	Few C, St	0	Few SA, St	0	...	.....		.....			
	C	++++	...	+++	Mod SA, St, D	0	Few C, St	0	Few SA	0	Mod SA, D, St	.....		.....			
		(8)		(3)		(1)		(7)		(19)							
8	A	+++	...	0	Few SA, D	+++	Mod SA, few D	+++	Few SA	0	Few bacteria	0	Ab SA, few St, D	.....			
	B	++++	...	0	...	++++	Few SA, C	+++	Few SA	0	Few bacteria	0	Ab SA, few St, D	.....			
	C	++++	Few SA	0	...	+	...	0	...	0	Many bacteria	0	Few D	.....			
		(28)		(25)		(14)		(7)		(2)		(21)					
28	A	0	Few bacteria	++	Few SA	++	Mod SA	0	... SA	0	Ab SA, St	++	Mod St, few SA	0	...		
	B	0	Few bacteria	+++	Few SA	0	Few SA	0	... SA	0	Ab SA, St	0	Few St, few SA	0	...		
	C	+	...	++	...	++	...	0	...	0	Mod SA, few St	0	...	0	...		
		(15)		(14)		(4)		(1)		(10)		(30)		(58)			
22	A	0	Ab SA, few St	0	Few SA, St	+++	Few SA	++	Few SA	0		0	Few SA	0	0 Few SA		
	B	0	Few St	0	Few SA, St	+++	Few St	+++	Mod SA, SAu, few St	0		0	Few SA	0	0 Few SA		
	C	0	...	0	...	0	Few SA, St	+++	Few SA, St	0		0	...	0	0 ...		
		(25)		(22)		(20)		(12)		(6)		(22)		(30)	(84)		
12	A	+++	Few SA, Ab D	+++		0	Ab SA	0	Overgrown	0	Ab St, few Py	0	...	.....			
	B	+++	Few SA, Ab D	+++		0	Ab SA	0	Overgrown	0	Ab St, few Py	0		.....			
	C	+++	Mod SA	+++	Few SA, GN	0	Few SA	0	Mod SAu, few C, St, few Py	0	Ab Py	0		.....			
		(23)		(21)		(1)		(22)		(42)		(62)					
31	D	+++	...	++++	...	.....		++	Few SA	+++	...	0	Few SA	A	0		
	E	.....		.....		0	...	0	Few SA	0	Few St	0		B	0		
		(0)		(1)		(55)		(64)		(71)		(97)		C	0		
															(347)		
43	A	0	...	0	Overgrown	++++	Mod SA	.....		.....		.....		.....			
	B	0	...	0	Overgrown	++++	Mod SA	.....		.....		.....		.....			
	C	0	Ab SAu	+++	...	+	Few SA	.....		.....		.....		.....			
		(0)		(3)		(8)											
32	D	++	...	0	Few SA	A	+++ Mod SA, Ab St	.....		.....		.....		.....			
	E	++	...	+	Few SA	B	+++ Few SA, few St	.....		.....		.....		.....			
		(0)		(10)		C	++ Mod SA, few St	.....		.....		.....		.....			
						(131)											
45	A	+++	...	++	...	0	Few SA, St	.....		.....		.....		.....			
	B	+++	...	++	...	0	Few SA, St	.....		.....		.....		.....			
	C	+++	...	+++	Mod SA	++		.....		.....		.....		.....			
		(0)		(1)		(14)											
47	A	++	Ab bacteria	0	Few St	0	Few SA, Ab St	0	Ab SA, Mod S	.....		.....		.....			
	B	++	Ab bacteria	++	Mod SA, St	0	Few SA, Ab St	0	Few D	.....		.....		.....			
	C	+++		+++	...	0	Few C	0	Few SAu, St	.....		.....		.....			
		(0)		(1)		(2)		(34)									

NOTE: Results of cultures for PPLO are indicated by 0 to ++++. SA = Staph. albus, SAu = Staph, aureus, St = streptococci, D = diphtheroids, C = B. coli. Py = B. pyo cyaneus.

* A = urethral loop, B = prostatic fluid, C = residual urine, D = urine after massage, E = urine before massage.

† The digits in parentheses are the number of days before or after treatment was begun. When two courses were given, the digits are the days after initiating the first course. For the five patients who were not treated, the digits are days after first being seen.

‡ Mod = moderate and Ab = abundant. The double vertical lines indicate a course of streptomycin therapy

had evidence of hydronephrosis secondary to edema of the ureteral orifices. In several of the chronic urethritis cases weight loss and fatigue were prominent enough to warrant extended hospitalization.

Cultures. Of eighty-eight patients studied, fifty-seven had positive cultures for PPLO. The thirty-one negative patients could be divided on the basis of later cultures into three groups: two patients with B. pyocyaneus (Pseudomonas aeruginosus); four with B. coli.; and 25 remaining patients without adequate cause (streptococci, staphylococci and diphtheroids only).

The fifty-seven patients with positive cultures for PPLO in many instances showed bacteria other than the pleuropneumonia-like organisms. However, thirty-three patients showed a pure culture for PPLO on at least one occasion and two others always had pure cultures. As would be expected, cultures from the urethra were more often contaminated than cultures from the bladder. In the eleven patients with cystitis the organism was found in pure culture at least once in five cases (Table II).

Incidence of PPLO in Cultures from Men without Presenting Symptoms of Genitourinary Disease. Of ninety-eight men studied as controls thirty-six showed positive cultures for PPLO, an over-all percentage of 36.7 per cent. This compares with 65 per cent (fifty-seven of eighty-eight) positive cultures in the patients with genitourinary complaints. This is a highly significant difference, ($P = <.001$) with χ^2 value of 14.6. Cultures in these groups were not strictly comparable. The first group of fifty-one patient controls had only single urethral loop cultures.

Only urine cultures were obtained in the patients first studied (D and E). If only those control subjects and patients are compared who had cultures (A, B and C) on the first attempt, and if only the results of the first culture from patients are included, there remain forty-seven separatees with sixteen positive cultures (34 per cent) and seventy-one patients with thirty-seven positive cultures (52 per cent). This difference is just within the limits of significance ($P = <.05$).

There was considerable evidence, however, that the control group did not actually represent a population with negative genitourinary histories and findings. The desired comparison was between men with evidence of genitourinary disease and those without such evidence. For this reason, and without knowledge of culture results, the supposedly normal control subjects were sorted into groups with definite, questionable, and negative genitourinary findings.

The results are shown in Table III.

If the separatees with questionable or negative genitourinary findings (twenty-three with five positive cultures, or 22 per cent) are compared with the thirty-seven patients with initial positive cultures, there is a significant difference by χ^2 calculations ($P = <.02$). There were no positive cultures in the eight separatees who had entirely negative genitourinary findings. If all controls are included the over-all percentage of positive cultures in the group with negative genitourinary findings is 18 per cent. However, the best estimate of the incidence of PPLO in a group entirely free of genitourinary findings is probably 22 per cent compared with 52 per cent in a group seeking medical care for genitourinary complaints. Whether this difference is due only to the presence of moisture and mucus in the urethra or indicates the pathogenic effect of PPLO cannot be decided.

Recent treatment with penicillin had no effect on the proportion of the control subjects with a positive culture. Recent venereal exposure could

TABLE III

INCIDENCE OF POSITIVE CULTURES FOR PPLO ORGANISMS IN AFFECTED SUBJECTS AND PATIENTS WHO DID NOT SEEK MEDICAL CARE FOR GENITOURINARY COMPLAINTS

		GU +	GU ?	GU −	
Positive for "L"	Patient controls	7	7	6	20
	Separatees	11	5	0	16
Totals		18	12	6	36
Negative for "L"	Patient controls	6	11	14	31
	Separatees	13	10	8	31
Totals		19	21	22	62
Grand Total		37	33	28	98

NOTE: GU + means a definite discharge, hematuria or severe dysuria of more than four days' duration, other than gonorrheal; or frank pus in the prostatic fluid (more than 10 white cells per high power field); or a grossly abnormal prostate. GU ? means minor symptoms, gonorrhea; or 5 to 10 white cells in the prostatic secretions, or a prostate described as slightly abnormal. GU − means no genitourinary symptoms, less than 5 white cells in the prostatic secretions, and a normal prostate.

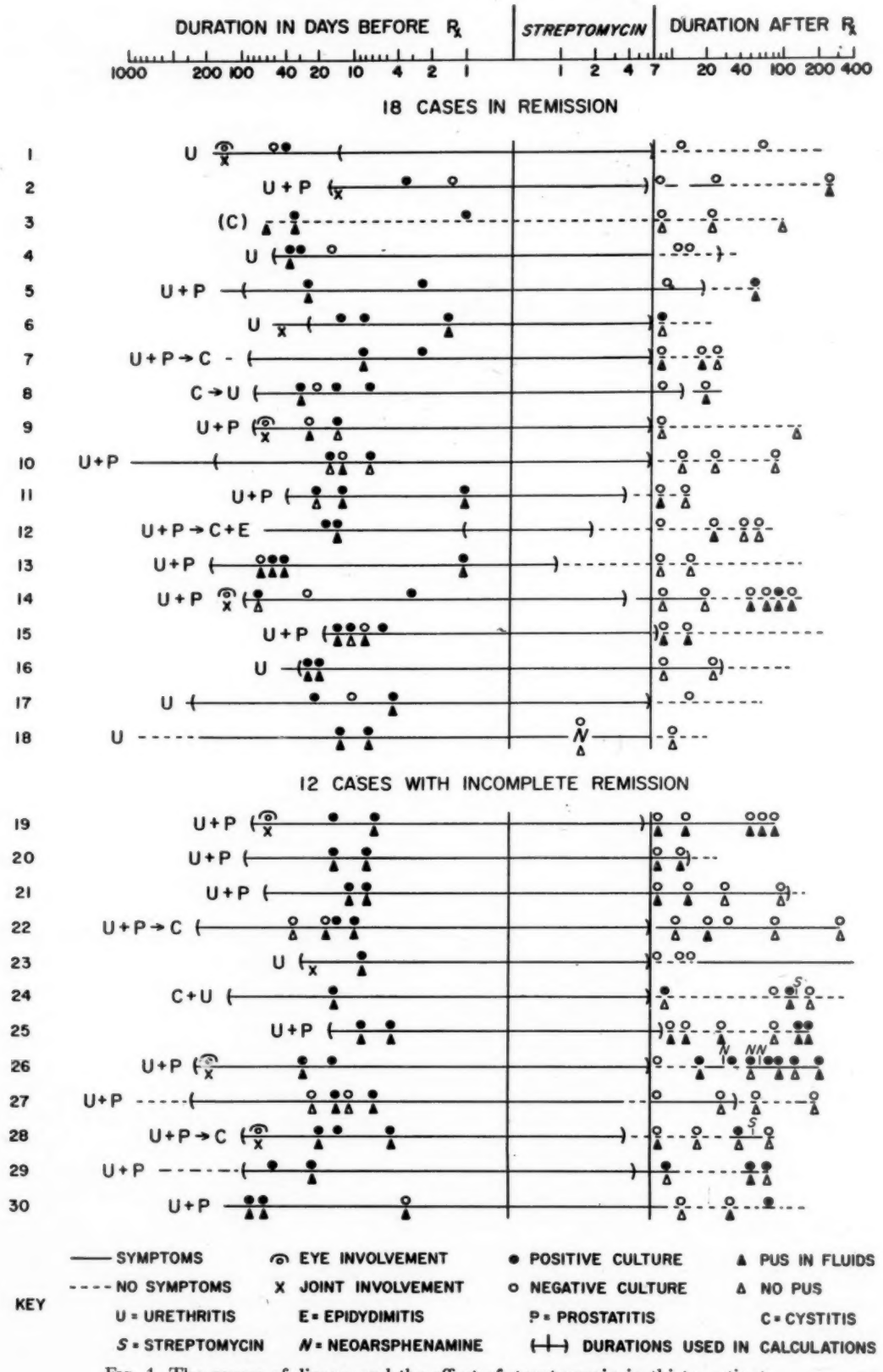

FIG. 1. The course of disease and the effect of streptomycin in thirty patients.

not be evaluated as a factor inasmuch as all but a few control subjects had been recently exposed.

Results of Streptomycin Therapy. The duration of symptoms in the thirty treated patients (one of these was treated with neoarsphenamine), and the change in symptoms during streptomycin therapy (2 gm. daily, 4 gm. if arthritis was present) are shown in Figure 1. A solid line represents any and all symptoms present.

By use of a technic reported elsewhere [*28*], the distribution of durations of disease was computed. It was found that a logarithmic correction was needed to avoid skewness.

The results may be tabulated as follows:

A	B	C
Per cent of Population	Total Duration (days)	Standard Deviation (range)
2.15	0–13	−3 to −2
13.59	14–40	−2 to −1
34.13	41–102	−1 to 0
34.13	103–209	0 to 1
13.59	210–379	1 to 2
2.15	380–644	2 to 3

The expected distribution of total durations of disease as calculated from incomplete durations of disease. Column B indicates how long the disease can be expected to last for each of the percentage groups indicated in column A.

With this information [*28*], it was evident that the remission of symptoms occurring during streptomycin therapy occurred much sooner than might have been expected by chance ($P = <.001$).

Toxic symptoms occurred in twenty-seven cases; one patient had none; information from a second patient was not available. In the remaining twenty-seven patients treated with streptomycin the symptoms included: numbness of the face, 25; dizziness, 16; anorexia, 13; headache, 9; sleepiness, 8; nausea, 7; lassitude, 6; tinnitus, 5; fever, 5; fatigue, 3; rash, 3; malaise, 3; vomiting, 2; joint aches, 2; toxic psychosis, 1; pruritus, 1; transient deafness, 1; cold sweat, 1; faintness, 1.

Patients with Negative Cultures for Pleuropneumonia-like Organisms. By comparison, the thirty-one patients with negative cultures for the pleuropneumonia-like organisms constitute a heterogeneous group. B. pyocyaneus was responsible for urethritis in one and for pyelonephritis in another. Moderate growths of B. coli were found in one case each of urethritis, urethritis and prostatitis, and pyelonephritis.

In most of these patients with negative cultures for PPLO a mixed flora of streptococci, staphylococci and diphtheroids was found. There were, in addition to the five cases already described, ten cases of urethritis, twelve cases of urethritis and prostatitis, one case of urethritis, prostatitis and cystitis, and one case of urethritis and cystitis. There were only four cases of cystitis in this group.

Only fourteen of these thirty-one patients went into remission during the period of observation, sometimes in association with penicillin or sulfadiazine therapy, sometimes only with supportive treatment. The symptoms in these fourteen cases had been of twelve days' to eighteen months' duration, whereas the persistent illnesses in the other sixteen cases were frequently of several years' duration.

Of the thirty-one negative patients, thirteen had had penicillin within two months.

COMMENTS

The Clinical Picture of Acute Hemorrhagic Cystitis. The findings referable to the bladder in our cases of cystitis are substantially the same as those reported in *abacterial pyuria* by Wildbolz [*3*], Söderlund [*1*], Runeberg [*2*], Schaffhauser [*4*], Hamm [*6*], and Bazy and Oudard [*14*]. Wildbolz, in particular, describes with care a disorder indistinguishable from these cases. The hemorrhagic character of the cystitis is evident from all these authors. Our patients were all men, but Wildbolz comments on its infrequency in women, and we have not seen cases of it in women in a mixed patient population over a period of several years. A number of cases appear in these reports in which the disease was of long duration.

Involvement of other parts of the genitourinary tract has occasionally been described. As early as 1909 Faltin [*15*] suggested that cystitis might follow a gonorrheal prostatitis. In Wildbolz's cases there was frequent infiltration of the prostate and seminal vesicles. Three of Hamm's seven cases were preceded by urethritis. Associated disease of the renal pelvis and parenchyma was studied by Runeberg [*2*] in ten cases of aseptic pyuria beginning with hemorrhagic cystitis which were not tuberculous. The histologic picture in these cases consisted of a

lymphoid infiltration with prominent follicles. Schaffhauser [*4*] found a similar associated chronic follicular pyelitis. Pain and tenderness in the costovertebral angle was seen in these cases and Moore found evidence in x-ray films of ureter and pelvis dilation and occasional filling defects.

The development of conjunctivitis, arthritis and changes in the skin in association with acute hemorrhagic cystitis has not been mentioned in previous reports of this disorder, although the association of hemorrhagic cystitis with Reiter's disease has been noted. These changes are likely to occur in patients with a prolonged course, especially during a second or later exacerbation (see abstracts F-I) [*16*]. The relation to the infection in the genitourinary tract seems probable, not only because of their concurrence but because of the acute appearance of conjunctivitis, for example, after manipulation of the prostate (Case 1, Fig. 1) or kidney (Case I, Appendix).

Joint and eye changes are well known as a complication of urethritis in Reiter's disease. Furthermore, involvement of the prostate and epididymis [*17*] during episodes of urethritis is common.

It is apparent that acute hemorrhagic cystitis in its clinical complications closely resembles isolated non-gonococcal urethritis. It seems probable that this type of infection of the bladder is a facet of a potentially generalized genitourinary tract infection, but that it presents an especially dramatic clinical picture because of the intense inflammatory response with which the bladder mucosa responds. Both upper and lower portions of the tract react in a more indolent manner. The infection often originates in the urethra, spreads to the genital appendages and to the bladder, may obstruct the urethral orifices by edema, and ascend into the kidney pelvis and parenchyma. Dissemination into the circulation may occur from any of these sites, with involvement of other organs.

The Infective Nature of Acute Hemorrhagic Cystitis. Abacterial pyuria presenting this picture has long been considered infectious [*2,3,15*]. The march of inflammation up the urinary tract, the remote involvement of other tissues, and the response to arsenicals, streptomycin and the tetracyclines leave little doubt of this.

The genitourinary tract, like the respiratory tract, is in open communication with the outside world and houses in its extremities a varied bacterial flora. All these various bacteria produce cystitis occasionally, although their pathogenicity varies. It is slight with diphtheroids, Staph. albus and fecal streptococci, which are almost always present in the urethra. It is more marked with Staph. aureus, B. coli and B. pyocaneus. It is likely that the PPLO has a potential pathogenicity similar to that of the other saprophytes. This is indicated by their presence in abscesses connected with the female genitalia and also occasionally in the blood and spinal fluid. The likelihood of pathogenicity is increased by the fact that similar organisms cause a variety of diseases in animals: agalactia in goats and sheep, pleuropneumonia and arthritis in cows, and arthritis and encephalitis in rodents.

The finding of PPLO in the urine in cases of cystitis which cannot be attributed to bacterial infection makes the etiologic role of PPLO very probable. The bladder is a sterile organ. Therefore any organism found in the urine may be regarded as the cause of cystitis. The effectiveness of streptomycin is further evidence of the etiologic role of the PPLO. This organism, like many others, can certainly produce infections of the bladder and of the upper urinary tract. The question which remains to be settled is whether or not it is the usual causative agent in the production of hemorrhagic cystitis.

The observation that in thirteen consecutive cases of this illness PPLO was present in eleven, in the absence of bacterial agents, indicates a positive answer. In the group of thirty-one patients from whom PPLO was not isolated there were only six cases of clinically definite cystitis, four of which were of bacterial origin. To obtain a definite answer it will be necessary to study more patients of different types and in different locations.

There are certain considerations which suggest caution. The most important is that we cannot be certain that an organism cultivated from the urine really originated from the bladder and not the urethra. This difficulty is solved in the case of bacterial infection by the fact that the bacteria are present in masses. This was true in some cases also with PPLO. The presence of this organism in the upper urinary tract was established by cultivation of urine obtained by aspiration from the renal pelvis during operation. However, we cannot be certain that the PPLO originated in all cases from the bladder.

Certain observations made in women also suggest caution. We have not observed any case in which acute cystitis could be attributed to PPLO

in women, although the organism is often present in the vulva. On the other hand we have observed two cases of tuberculous infection in which PPLO was present in the urine in women. Elimination of these organisms with streptomycin had no effect on the symptoms. Certain pathologic conditions, independent of the PPLO, may apparently promote the establishment of this organism in the bladder. It is not possible at present to form an opinion as to the pathogenic significance of PPLO in the urethra.

A number of investigators have reported attempts to cultivate PPLO from presumably healthy males [*7,8,9,17–24*]. The percentage of positive cultures has varied from 0 to 36 per cent. There is suggestive evidence that the proportion of positive cultures is related to the degree of promiscuity [*23*]. The reports indicating a small percentage of positive cultures have been of groups with restrained venereal contacts including sixty-seven Australian medical students with no positive cultures [*20*], fifty English "normal males" with no positive cultures [*25*], fifty-five white medical students with 2 per cent positive cultures [*23*], and ninety British police officer candidates with 11 per cent positive cultures [*24*]. A higher percentage of positive cultures was obtained from the present series of sailors; only four of ninety-seven had not had recent casual exposure, and 36 per cent of these had positive cultures. Thirty-three per cent of fifty-seven colored college students [*23*] had positive cultures.

By comparison, in some series the percentage of positive cultures in patients presenting with genitourinary complaints appears little different from that of normal control subjects [*21,22,26*]. Even in series with a substantial difference between control subjects and patients [*23,25*] the high values found in the control subjects are puzzling. It is apparent, however, that a comparison between healthy males and patients is justifiable only if they represent a similar population. If venereal exposure plays an important role, then a sexually circumspect population cannot be compared with a sexually promiscuous population. In the present study the two populations investigated are as similar as it is possible to obtain, and a significant difference in the proportions of positive cultures for PPLO has been observed.

It has been suggested by Shepard, Nicol and Edwards, and others, that PPLO are commensals, non-pathogenic saprophytes without significance in non-specific genitourinary infections. This is a possibility that cannot be excluded. As has been pointed out, however, there is a highly significant difference between the percentage of positive cultures in control subjects and patients. If control subjects with genitourinary abnormalities were excluded the percentage of positive cultures would be halved. Furthermore, the PPLO tend to disappear with remissions (spontaneous and therapeutic) and to return with exacerbations. This does not constitute proof that the PPLO is the causative agent. It does suggest the PPLO is associated with the disease process. The simplest conclusion is that they sometimes cause disease, that the disease is acquired from promiscuous partners, that initial infections may be minimal and unobserved, that after initial infections the organism may remain in the host living on mucosal surfaces in spite of host resistance to its potential pathogenicity. For this last point there are numerous examples found in carrier states in the respiratory tract. They may have much the same significance as meningococci occurring in the nasopharynx during epidemic circumstances, except that promiscuity at any season presents the necessary conditions for epidemic spread of urinary tract infection.

Effectiveness of Streptomycin. In the treatment of non-gonococcal urethritis, penicillin and sulfonamides have generally been ineffective [*17,26*]. The tetracyclines and chloroamphenicol have proved effective, [*17,27*] as has streptomycin. Harkness obtained only 55 per cent cures with streptomycin but he used a dose of only 1 gm. daily.

Most strains of PPLO are sensitive to streptomycin, but a few colonies often develop on the plates even with 50 units per ml. of the medium. The efficacy of streptomycin varies also in patients. We have studied a few patients at the Massachusetts General Hospital in whom it was not possible to eliminate PPLO either from the urethra or from the bladder with streptomycin, although the clinical condition improved during the treatment. Considering that cures cannot be expected with streptomycin in 100 per cent of the cases the results obtained in the present study are impressive.

CONCLUSIONS

1. Fifteen cases of acute hemorrhagic cystitis ("acute abacterial pyuria") are described. Involvement of both upper and lower portions of

the genitourinary tract and of eyes, joints and skin may accompany the cystitis.

2. It is suggested that pleuropneumonia-like organisms (PPLO) are the infective agent of this disorder in view of their presence in urine cultures, the absence of other bacterial organisms to which the condition could be attributed and the disappearance of PPLO during successful antibiotic therapy.

3. The incidence of PPLO in a control group was 35 per cent; if only those with entirely negative genitourinary findings are considered, 17 per cent had positive cultures.

4. Of eighty-eight patients sick with nongonococcal genitourinary complaints 65 per cent had positive cultures of PPLO; 52 per cent if only first cultures were included.

5. In addition to a probable role in the etiology of acute hemorrhagic cystitis, pleuropneumonia-like organisms possibly are responsible for many cases of non-gonococcal urethritis and prostatitis. It is likely that the organisms are transmitted venereally, that they are thus present with much greater frequency in promiscuous males, and that after an initial infection they may linger asymptomatically in the urethra or prostate.

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APPENDIX

NAVY SERIES

CASE 7. Two months before admission a urethral discharge developed in this twenty year old sailor within a day or two after venereal exposure. Smears were negative for gram-negative intracellular diplococci and it cleared spontaneously. Two weeks prior to admission he passed cloudy urine terminating with a few drops of gross blood. There was a "bearing down" feeling in the lower abdomen, urinary frequency and burning, and a weight loss of 10 pounds.

On admission the urine and prostatic fluid were abounding with white blood cells, and the blood leukocyte count was 12,000 per cu. mm. Cystoscopy showed injection of the posterior urethra, many minute cyst-like blebs over the entire bladder mucosa, and two small cysts at the internal sphincter. Many large white shreds floated freely in the bladder urine. Urine cultures were positive for PPLO on two occasions, once in pure culture. Administration of sulfonamides and penicillin was without effect. Two months after admission he was treated for one week with streptomycin, 2 gm. daily. Symptoms cleared and cultures were negative by the first day after completion of therapy and the urine was clear a week after. The prostatic fluid contained many white blood cells at this time but only 10 to 15 cells nineteen days after completing treatment with streptomycin. He remained asymptomatic.

CASE 8. One month prior to admission and without venereal exposure for one year, this nineteen year old sailor noted the onset and increasing severity of burning frequency, nocturia and cramping suprapubic pains. Four days before admission he passed a large piece of whitish membrane followed by a few drops of pinkish urine. A scant, thin, watery urethral discharge appeared the following day.

On admission the prostate was firm and nodular and the fluid contained 30 to 35 red cells. The urine contained many white blood cells and 4 to 6 red blood cells. Three weeks after admission a transient follicular rash appeared. Cystoscopy showed acute membranous and hemorrhagic cystitis. Pure cultures of PPLO were obtained from urethra, prostatic fluid and urine on one occasion each. Six weeks after admission, following ineffective penicillin and sulfadiazine therapy, he was treated with 2 gm. of streptomycin daily for one week. Two days after the last dose of streptomycin had been administered the urine and prostatic fluids were negative for pus and PPLO. Five days after, he was asymptomatic. One week after discontinuance of streptomycin therapy there was a recurrence of hematuria and burning lasting two weeks, which then cleared. Cystoscopy at this time showed only injection of the posterior urethra.

CASE 12. This twenty-two year old, married Negro sailor noted a scant whitish urethral discharge two weeks after extramarital exposure. Ten days after admission a lower abdominal cramping pain developed, sometimes radiating to the penis and scrotum. For one week he noticed terminal hematuria, although at first the urine was grossly red. He had been nauseated for four days.

On admission slight tenderness was noted in both lower quadrants and in both flanks. The prostate was nodular and large. The urine sediment contained 3 to 5 white blood cells and the prostatic fluid 15 to 20 white blood cells. Urine and urethral cultures grew out PPLO colonies mixed with a few Staph. albus. Cystoscopy revealed prominent vessels in the bladder with sanguinous urine. Acute trigonitis and posterior urethritis, with chronic anterior urethritis, were noted.

Although the hematuria and discharge largely cleared spontaneously, the prostatic fluid continued,

with many white blood cells. One month after admission an acute epididymitis developed and the following day a one week course of streptomycin, 2 gm. daily, was begun. The testicular pain and induration cleared on the second and fifth days, respectively. Three and one-half weeks after concluding streptomycin therapy he was asymptomatic, and cultures showed no PPLO. The prostatic secretion was negative two weeks later. He remained asymptomatic two and one-half months after therapy.

CASE 22. Nine months prior to admission this nineteen year old sailor noted a urethral discharge of two days' duration, without venereal exposure. Three months thereafter a thick urethral discharge appeared the day after exposure, and it became watery in a few days. For four months there had been frequency and burning on urination. Administration of penicillin and sulfadiazine had no effect. For two months the urine was cloudy, the eyes were sore and granular, and he experienced occasional pain in knees and ankles.

On admission, cystoscopy showed a diffusely injected, granular posterior urethra, and a whitish mucoid membrane overlying the bladder mucosa. The prostate was slightly nodular, and the fluid contained 10 to 15 white blood cells. PPLO were obtained from the urethra and urine, mixed with very few Staph. albus and non-hemolytic streptococci. Six weeks after admission he was treated with 2 gm. of streptomycin daily for one week. On the final day of treatment he was asymptomatic. There was a recurrence of discharge two days after completing streptomycin therapy. Repeat cultures were negative for PPLO. Minor symptoms persisted when last seen two months after completing streptomycin therapy.

CASE 24. Three months prior to admission this nineteen year old sailor was venereally exposed and thirteen days later a scant urethral discharge developed, negative for gram-negative intracellular diplococci. After two weeks frequency, hesitancy, nocturia, dysuria, temperature to 101°F., bloody urine and postperineal nocturnal deep penile pain developed. His prostatic fluid was loaded with white cells. He had many red cells and white cells in his urine, and a white blood cell count of 16,000 per cu. mm. He was admitted for study after several incomplete remissions and exacerbations and ineffective sulfonamide therapy, having lost twenty-five pounds in weight since the onset.

On admission the prostate was slightly nodular. Cystoscopy showed an extremely spastic bladder, membranous sloughs, especially in the trigone which presented an inflamed base. The ureteral orifices were edematous and bled easily. His temperature rose as high as 103.4°F. Perineal pain became so severe that morphine was required for relief. There was no response to penicillin. Six weeks after admission a week's course of streptomycin (2 gm. daily) was begun after finding PPLO in pure culture in the urethra, urine and prostatic fluid. By the second day there was a dramatic decrease in all symptoms, and by the end of the week he was asymptomatic. Repeat cystoscopy showed well-advanced healing. Cultures were now negative.

Three and a half months after admission, he passed several fragments of clotted blood during a single day without symptoms. Six months after admission there was a recurrence of urethral discharge, burning, frequency and gross hematuria. Cultures were again positive for PPLO in pure culture. A second course of streptomycin was given in dosage of 4 gm. daily for one week. Improvement was noted on the fourth day and he was asymptomatic by the sixth day. Cultures were then negative for PPLO except for a pure growth in the urethral loop two months later. He had remained well when last seen four months thereafter.

CASE 28. Seven weeks prior to admission and seven days after venereal exposure this twenty-two year old sailor had a urethral discharge associated with an itching sensation, burning, frequency and urgency. On admission the prostate was nodular and tender. Smears were negative for gram-negative intracellular diplococci. Penicillin and sulfathiazole had no effect. Cystoscopy revealed a fiery red bladder and posterior urethra mucosa with membranous sloughs. Cultures of the urine were positive on three occasions for PPLO in pure culture. Four weeks after admission he was treated with 2 gm. of streptomycin daily for one week. He was free of symptoms and pus by the fifth day and cultures were negative. One month after streptomycin he had recurrent discharge, burning and intense bladder injection. Aching and stiffness in the low back, right shoulder, upper arms, lower legs and right wrist developed. He lost 10 pounds of weight in the following two weeks. Six weeks after completion of the first course of streptomycin he was given a second course of 4 gm. daily for one week. Within twelve hours there was marked relief of joint pains. The discharge cleared on the sixth day and he was entirely asymptomatic on discharge one week later; cultures were negative for PPLO.

CASE 31. Three months before admission this twenty-nine year old married sailor noted a purulent discharge two weeks after marital exposure. The discharge did not change during penicillin and sulfadiazien therapy but cleared spontaneously on the tenth day of symptoms. One week before entry frequency, dysuria (terminal especially), attacks of severe retroscrotal pain following urination and a coronal papule developed.

On admission, cystoscopy showed a white membraneous slough on an inflamed base in the region of the trigone, involving the ureteral orifices and obscuring the left orifice. The posterior urethra was inflamed. Cultures of the urine were positive for PPLO in pure culture on three occasions. The pain persisted for several weeks although with gradual improvement.

Fourteen weeks after entry he was asymptomatic and cultures for PPLO were negative. Many white blood cells persisted in the urinary sediment. He had remained well when last seen twelve months after hospital study; cultures remained negative for PPLO.

CASE 32. One and one-half months before admission this nineteen year old sailor had a thick urethral discharge, one month after venereal exposure. The discharge soon became watery and cleared during a two and a half week's course of penicillin and sulfadiazone. Nine days before admission he noted a few drops of blood after urination, with associated sharp burning pain suprapubically, and in the penis and posterior perineum. Administration of penicillin and sulfonamides had no effect. For four days the urine was grossly red with clots; there was uncontrolled urgency (including voiding in bed) and frequency (three times an hour).

On admission the patient was in acute distress. There was a papular eruption on the penis. The urine contained many red cells and white cells with much albumin. Cystoscopy showed diffuse congestion of the bladder with large white membranous sloughs. The trigone and ureteral orifices were red and edematous. Cultures of the urine were positive for PPLO in pure culture on one occasion and mixed with a few Staph. albus on other occasions. Symptoms cleared after several days of silver nitrate instillations. Five weeks after entry he had pain and swelling in the left wrist, and plantar vesicles were observed on the right foot. These cleared rapidly and he remained asymptomatic three months later, although PPLO persisted in cultures of the urethra, prostatic fluid and urine.

CASE 43. Four weeks prior to entry this nineteen year old sailor had been treated with penicillin for gonorrhea, with complete clearing of symptoms. Five days before admission terminal hematuria, burning on urination, and marked frequency (twenty times daily) developed. This persisted for three days and he was then asymptomatic except for a feeling of distention in the lower abdomen. On admission there was moderate suprapubic tenderness. The prostate was large and unusually firm. The urine contained clumps of red cells and white cells and 4+ albumin. Prostatic fluid contained many white cells and red cells. Cystoscopy showed a diffusely injected bladder with free floating mucous shreds. The posterior urethra was moderately injected. There were a few petechiae in the anterior urethra. From the urine PPLO were cultured, sometimes in pure culture and sometimes mixed with Staph. albus. He was discharged without specific treatment. Five months later he remained asymptomatic. Urine and prostatic secretions were normal.

CASE 45. This thirty year old sailor had a urethral discharge four weeks before admission, after recent venereal exposure. Ten days before entry he noted grossly bloody urine. On admission the prostate was large, firm and tender. There was a single red macule on the corona; the urine was loaded with white cells and contained 3+ albumin. Cystoscopy revealed hemorrhagic areas with a central slough in the bladder, and posterior urethritis. The prostatic fluid was loaded with white blood cells. PPLO grew profusely in pure culture from the urine, urethra and prostatic fluid on one occasion, and mixed with a few Staph. albus on the second and third cultures. Within three days after entering the hospital the hematuria subsided and the discharge disappeared without specific therapy. PPLO persisted in the urine culture.

CASE 47. This twenty-one year old sailor noted burning on urination and a urethral discharge the day before admission, and ten days after venereal exposure. On admission the prostate was slightly nodular, and the fluid contained 5 to 10 white blood cells. Cystoscopy showed the posterior urethra and bladder to be diffusely injected. The urine culture showed a pure growth of PPLO on two occasions. In the course of the next month his symptoms abated, and cultures became negative for PPLO. Four months later he was well except for infrequent burning on urination.

OTHER CASES

CASE A (No. 54213). Two months prior to admission this forty-nine year old, married, restaurant manager noted the onset of a urethral discharge. Four days after onset he was awakened at night by profuse urethral bleeding. After this subsided there appeared burning on urination, frequency and terminal hematuria. Although the discharge subsided the other symptoms persisted to the time of admission, and the urine was cloudy. Twenty years previously he had had gonorrhea with early remission. Fifteen years previously a urethral discharge responded within two weeks to conservative treatment.

On physical examination the prostate was small, firm and non-tender. Cystoscopy revealed a fiery red bladder mucosa. The bladder urine was thick and purulent, and contained many fibrin shreds. There were 12,200 white blood cells in the peripheral blood with 79 per cent polymorphonuclears. The urine was loaded with white blood cells and 2+ albumin. A single urine culture showed abundant B. coli. Others were negative except for the finding of abundant growth of PPLO in pure culture.

On a regimen of 2 gm. of streptomycin daily there was a prompt reduction in severity of symptoms, and at the end of ten days of treatment he was asymptomatic. Cultures for PPLO remained negative after the third day of therapy. He was discharged with a diagnosis of cystitis and prostatitis. Two years after the first admission the patient returned to the hospital with a three weeks' history of recurrent urethral discharge accompanied by burning, frequency and nocturia. Sulfonamides and penicillin therapy had

been tried without success, and urine cultures were again positive for PPLO. Physical examination showed a moderately enlarged, firm, non-tender prostate. The white blood cell count was 18,000 with 78 per cent polymorphonuclears. The urine contained 2+ albumin and 30 to 75 white blood cells in the sediment.

Streptomycin (2 gm. daily) and penicillin (300,000 units daily) were given for eight days. He was asymptomatic by the fifth day of treatment and was discharged with the diagnosis of cystitis, prostatitis and urethritis.

CASE B. This twenty-one year old sailor contracted gonorrhea two and one-half years before admission to the hospital. This responded to sulfonamide treatment but two months later a profuse urethral discharge developed and this was soon accompanied by terminal hematuria. There was 3+ albumin in the urine, and it was loaded with white cells and red cells. Cystoscopy two months later showed marked edema and redness of the bladder mucosa and a "golf hole" appearance of the ureteral orifices. A catheter could be passed no further than 2 cm. up the left ureter. He was much improved while receiving sulfadiazine for this disorder and mapharsen for warts on his hands.

One and one-half years prior to admission he was seen for a recurrence of hematuria, frequency, nocturia, and a weight loss of 40 pounds. He had had several recurrences of urinary frequency, urgency and enuresis (an old complaint) since first being studied. His urine was grossly bloody. Cystoscopy showed an acute diffuse cystitis with numerous ulcerations, some of which had necrotic centers. Both ureteral orifices were edematous. The left ureter could not be catheterized. Retrograde pyelograms showed dilatation of the left renal pelvis, and the left lower ureter was constricted with dilatation above it. An intravenous pyelogram soon thereafter showed bilateral dilatation of the renal calyces and pelves; the ureters were not visualized. He had an episode of acute right epididymitis. His symptoms persisted until treatment with neoarsphenamine (0.3 gm. intravenously daily for two weeks). He was free of symptoms at the completion of this treatment.

Seven months before admission he was again seen because of recurrent frequency and urgency of several months' duration. The urine contained 2+ albumin and many white cells. There was voluntary rigidity in the lower abdomen. An intravenous pyelogram showed poor filling of the right renal pelvis. Cystoscopy showed injection of the posterior urethra and of the bladder mucosa. On the left the ureteral catheters could not be passed beyond 12 cm. His symptoms subsided somewhat during treatment with penicillin.

Two months before admission a recurrent urethral discharge developed associated with purulent balanitis and conjunctivitis. Cultures of the prostatic secretions were positive for PPLO.

CASE C. This twenty-one year old, single student, a veteran, noted the gradual onset of dysuria and terminal hematuria two months before admission. There was urinary frequency and nocturia twice nightly. Dull suprapubic pain was present before, during and especially after urination. Penicillin and sulfonamide therapy had no effect. There was no history of gonorrhea or syphilis, and there was no urethral discharge.

The physical examination on admission was entirely negative. The white blood cell count and hemoglobin were normal. The urine sediment was loaded with white cells and occasional red cells. There was 1+ albumin. Cystoscopy showed a diffuse inflammatory process of a scarlatiniform pattern involving the entire bladder mucosa, with several small ulcerations. The ureteral orifices were not involved. Guinea-pig inoculations were negative for tuberculosis.

There was questionable improvement on a combination of penicillin and sulfonamide therapy. He was discharged from the hospital after two weeks. Urine cultures were positive for PPLO. Six weeks after discharge, and three days after discontinuing penicillin and sulfonamide medication, he had a severe exacerbation of symptoms. The pain was increased particularly after physical activity, and radiated from the suprapubic area to the tip of the penis. There was terminal hematuria. He was readmitted to the hospital. The physical examination was negative. The urine had ++ albumin and the sediment was loaded with white and red cells. Blood counts were normal. He was given 300,000 units of streptomycin intramuscularly every four hours for eight days. Dizziness and numbness of the face were controlled with benadryl.® On the fourth day of treatment the urine sediment was negative, and he was asymptomatic by the sixth day. He remained asymptomatic on discharge, five days after completion of therapy.

CASE D. A sixteen year old student was first seen in the clinic because of a three months' history of frequency, burning, terminal hematuria, and the passing of a small crumbly stone (mixed phosphates and urates). There was no costovertebral angle tenderness and the blood calcium, phosphorus, and alkaline phosphatase were normal. The intravenous pyelogram was negative. The urine contained ++ albumin and numerous red and white cells. His symptoms partly remitted and recurred during the next three years, but he was admitted to the hospital on three occasions between the age nineteen and twenty-two with severe exacerbations. With these there was frequent suprapubic pain, and occasional flank pain with radiation to the groin, testicles and penis. There was occasional slight fever and weight loss and moderate leukocytosis. The prostate was enlarged and tender. Repeated cystoscopies showed varying degrees of "acute en-

crusted cystitis" with white plaques of membranous slough throughout the bladder, chiefly in the base, sometimes with angry red ulceration. At age twenty-two "golf hole" retracted ureteral orifices were seen. Most intravenous pyelograms were negative but a markedly dilated ureter and pelvis was seen on the right on one occasion. Numerous urine cultures showed no persistent or predominant organism, although B. coli was abundant in some cultures. Treatment with potassium permanganate instillations gave temporary relief. Penicillin and sulfonamide therapy had no effect. Streptomycin in doses of 2 gm. daily, or neoarsphenamine in doses of 0.3 gm., provided prompt although temporary improvement.

At age twenty-four he came into the hospital with an acute rectal abscess, spontaneous nosebleeds and fever. After drainage the abscess healed promptly but the urinary findings were still conspicuous. As usual between symptomatic exacerbations, however, he felt generally well. On this admission, while being treated with small doses (1 gm. daily) of streptomycin, he was found to have abundant growth of PPLO in seven consecutive urine cultures. In the initial plate cultures several individual tiny PPLO colonies could be seen microscopically to be growing out from single desquamated mucosal cells. He again improved after bladder instillations while receiving mandelic acid by mouth.

When twenty-five years old he was seen for an acute blepharoconjunctivitis in the right eye. When last seen one year later he felt well, but still had rather constant bladder pain especially on urination.

Case E (No. 532255). Three years prior to admission this twenty-six year old advertising salesman noted a whitish urethral discharge and urinary frequency while on a transport bound for Europe. While abroad he had numerous episodes of urinary frequency unaccompanied by dysuria, and the urine was said to be infected. In the two months before admission he was treated for terminal hematuria, and on entry had urinary frequency every forty-five minutes. An ischiorectal abscess drained eight years before admission.

On admission the physical examination was negative except for the presence of two small inflamed polyps at the urethral meatus. Urine contained ++ albumin and was loaded with red and white cells, hemoglobin was 7.0 gm. per cent, and the white blood cell count was 12,300 with 57 polymorphonuclears, 35 lymphocytes, 5 monocytes, 2 eosinophils and 1 basophile. The serum non-protein nitrogen was 11 mg. per cent. An intravenous pyelogram showed trabeculation of the bladder. By urine culture, numerous PPLO colonies were found and rare streptococci and diphtheroids. He was treated with 2 gm. of streptomycin daily for ten days and was symptom free and culture negative on the fifth day of treatment. He continued well at the time of discharge five days after completion of therapy. The diagnosis was acute cystitis.

Case F (No. 440884). Thirteen weeks before admission, and thirty-six hours after extramarital intercourse with the same partner for the second time (the first was six weeks previously) this twenty-six year old physician had a slight yellowish urethral discharge. He treated himself with sulfonamides, having observed organisms resembling the gonococcus on smear. There was little change, and ten weeks before admission there appeared marked burning on urination, frequency and incontinence. After two weeks there was terminal hematuria persisting for three weeks and marked urgency, worse on standing. Five weeks prior to entry lumbosacral backache and red conjunctivae with purulent discharge developed. Five days before admission he noted pain in the right ankle and, two days later, swelling. Pain also appeared in right shoulder and left elbow.

On admission there was some conjunctival injection, enlarged submandibular and supraclavicular nodes, slight tenderness over the left olecranon. The right ankle was red and moderately swollen with some increase in joint fluid. The white blood cell count was 14,000 with 73 per cent polymorphonuclears, 4 lymphocytes, 20 monocytes and 3 eosinophils. The urine contained + albumin but contained numerous colonies of PPLO as did the prostatic fluid. A tap of the left knee joint showed a sugar of 94 mg. per cent (serum 98 mg. per cent) with a viscosity of 11.9 at 38° and mucin that precipitated with small flecks and ropy clumps leaving a clear supernatant. On smear there were no organisms and 20 to 25 white cells per high power field with no clumps. The cultures were negative. Intravenous pyelogram showed moderate hydronephrosis of the calyces and ureters bilaterally. The serum non-protein nitrogen was 24 mg. per cent.

In spite of a course of penicillin (210,000 units in one day) symptoms were unchanged. Temperature of 101°F. was common in the evening for ten days. Eight days after entry marked herpes of the upper lip developed, and over the course of four weeks he had temporary discomfort in the right wrist and ankle, and right second metacarpal-lesser multangular joint. Marked atrophy of the flexors and extensors of the left leg was noted. He was discharged after six weeks' hospitalization, much improved; and two months thereafter he was symptom-free. Five years after discharge he was seen in follow-up and was asymptomatic except for mild discomfort in the right ankle and left knee in damp weather.

Case G (No. 557819). For a number of years this forty-three year old married cashier had had occasional left flank pain associated with hematuria. Three years prior to admission he had acute left flank pain of three hours' duration in association with chills and temperature rise to 103°F. He was treated with sulfonamides and penicillin. Since this first attack there had been three other similar episodes, and between attacks occasional aching in the left lower back. He

had noted initial hematuria on five occasions, and polydipsia, polyuria and nocturia. For about the same period of time he had noted occasional aching and stiffness in the shoulders and neck. Two years before admission he had noted a purulent conjunctival exudate with much conjunctival reddening, of one week's duration.

At the time of admission, the spleen was found to be palpable. The white blood cell count was 24,200 with 83 per cent polymorphonuclears. The twenty-four-hour urinary calcium excretion was 103 mg. on a restricted calcium diet. The urine showed 25 white cells in a spun sediment, with occasional red blood cells. A flat abdominal film showed bilateral mottled calcification throughout the caliceal and tubular areas of the kidneys. The serum calcium was 9.0 mg. per cent and the phosphorus 3.3 mg. per cent. Cultures of the urine were repeatedly positive for PPLO.

A course of streptomycin was given in doses of 2 gm. daily for nine days. By the third day the cultures became negative for PPLO and remained so. He was discharged, improved, on the fifth hospital day. The diagnosis was bilateral nephrocalcinosis and pyelonephritis.

CASE H. This twenty-two year old, married, insurance broker consulted his physician for a urethral discharge of seven months' duration. Previous to his marriage, during a period of considerable alcohol consumption, there was a first episode of urethral discharge of some weeks' duration. One month prior to his first visit the discharge reappeared but seemed to subside after ten days treatment with sulfadiazine. He complained of vague discomfort in the region of his prostate accompanied by a sense of urgency. The urine contained a few white cells. One month later frequency, urgency and dysuria persisted, and he was treated with sulfathiazole in conjunction with methylene blue. At about this time severe dysuria and terminal hematuria developed. Following a course of penicillin the patient appeared improved. At the end of this time cultures for bladder urine were negative for tubercle bacilli but positive for PPLO. Intravenous pyelograms were normal. Two months after the first visit tenderness, swelling and local heat in the right knee developed, which cleared with penicillin therapy. The whitish cells persisted in the prostatic fluid and he was treated with frequent prostatic massage.

Seven years after the first visit there was a recurrence of urethral discharge, which showed phenomenal improvement with chlortetracycline. Two weeks thereafter he experienced tender swelling of the right forefinger for which colchicine was given. Eight years after the first visit he had a recurrence of prostatitis which responded promptly to tetracycline. The diagnosis was chronic prostatitis and acute hemorrhagic cystitis.

CASE I (No. 221883). This thirty-two year old, married factory worker first noted red urine (for two days) five years before admission to the hospital. It was associated with no other symptoms but six months later he was studied in the hospital for reddish urine of a week's duration. There were small blood clots after urination and severe crampy suprapubic pains radiating to both flanks. He had marked urinary frequency, nocturia and urgency, and a burning sensation at the tip of the penis. There was mild, deep tenderness in the right lower quadrant; the prostate was enlarged, boggy, and very tender. The vesicles were enlarged and tender. The urine was loaded with red and white cells, and had +++ albumin. Phenolsulfonephthalein excretion totaled 60 per cent in two hours. The white blood cell count was 12 to 20,000 and the hemoglobin was 70 per cent. The skin reaction to old tuberculin (1:1000) was strongly positive. As on numerous later occasions guinea-pig inoculations were negative. Because of a deformed and dilated right renal pelvis a right nephrectomy was performed. The kidney showed evidences of hydronephrosis and chronic pyelonephritis. Within three months, evidences of obstruction to the left kidney developed, and because of persistent dysuria, terminal hematuria and pyuria, a left nephrostomy was established. During this interval an acute suppurative conjunctivitis developed (the day after the right nephrectomy) associated with pain, acute redness and swelling in the right ankle and knee. There was swelling of the lachrymal glands. Thick scaling lesions of the feet appeared. About two months after the nephrostomy it closed spontaneously. Some frequency and burning persisted, with occasional enuresis (present since childhood).

Three years before admission there was an acute exacerbation of burning on urination associated with suprapubic cramping pain and costovertebral angle tenderness. At about the same time he noted photophobia, a slight purulent discharge, and a burning sensation in his eyes. The anterior chamber was loaded with cells. The prostate was boggy and tender. An intravenous pyelogram was negative. There were scattered white cells in the prostatic secretion. The symptoms persisted for several months, occasionally recurring thereafter.

Six months before admission, he had a laparotomy for an acutely inflamed appendix. The prostate was as before, but the urine was negative. One week before admission there was a severe exacerbation of burning on urination, terminal hematuria, frequency and nocturia. There had been a weight loss of 10 pounds in the preceding month. These symptoms followed shortly after a period of alcoholic and sexual excess. Shortly before admission he passed blood clots at the end of urination. He had low back pain, and redness of the eyes with discharge.

On examination he appeared ill. There was an acute conjunctivitis on the left. There was marked tenderness over the right sacroiliac joint, and pain was accentuated on walking. There was tenderness of the left epididymis. A white creamy urethral discharge

was especially evident after prostatic massage. The urine had ++ albumin, occasional red cells, and was loaded with white cells. The white blood cell count was 14,300. The sedimentation rate was 1.51 mm./min. The urine revealed a pure culture of PPLO. During hospitalization pain developed along the costochondral junctions on the left, especially of the third and fourth ribs. Shortly after an urticarial reaction to sulfadiazine he was noted to have large hemorrhagic vesicles of the feet. His symptoms gradually diminished, and he was discharged much improved after four weeks.

He was seen again two years later with a pinworm infestation which responded after two courses of gentian violet. He had had repeated respiratory infections and had some pain and tenderness over the metatarsal heads of the left foot. He had had no urinary tract symptoms since a few months after discharge from the hospital.

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Klebsiella Meningitis*

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MENINGITIS due to klebsiella is one of the less common etiologic types. At the Philadelphia General Hospital (Blockley Division) it constitutes only 1.5 per cent of all cases of meningitis. However, since it has a rather poor prognosis its therapy assumes much significance.

We have reviewed the world literature on this subject, finding a total of 140 cases, to which we are able to add eleven cases seen at this institution between 1936 and 1956. The first 119 cases were summarized by Thompson [*1*]. It is the purpose of this report to summarize an additional twenty-one cases in the literature [*2–15*] and the eleven cases seen at the Philadelphia General Hospital, to discuss klebsiella meningitis in relation to capsular serotypes, and to attempt to deduce the therapy of choice from the available information.

METHOD AND MATERIAL

The records of all cases of bacteriologically proved klebsiella meningitis at the Philadelphia General Hospital (Blockley Division) from 1936 to 1956 were reviewed and the pertinent data are summarized in Table 1. Identification of the organism included capsular typing in most cases, but antiserums for types 1 and 2 (A and B of Julianelle) were the only ones available up to January, 1953. Thereafter antiserums for Types 1 to 10 were available.

RESULTS

Results of this study are presented in Table 1. The patients ranged from thirty-five to eighty years of age and ten were males. Three of the patients were Negroes and eight were white.

Probable Primary Focus. In six cases the focus of infection seemed evident: the middle ear in three, the lung in two, and the frontal sinus in one (hypophysectomy was performed through this area in this case). In the remaining five cases there was evidence of recent trauma to the head in four and trauma to the lower urinary tract in the other.

Bacteriologic Data. In six cases the organism could be demonstrated on direct smear of the spinal fluid and in one case typing was done at the time of the smear on the fresh spinal fluid. Recorded information indicated that the organisms cultured from the spinal fluid were typed in seven cases. Of these, six were types 1 or 2 and one was type 8. The latter occurred in the patient who suffered trauma to the lower urinary tract. In two cases blood cultures were reported and both of these were positive for klebsiella. In the five cases which came to autopsy, metastatic abscesses were noted in three, with involvement of the following organs: the kidney in two, the liver in one, and the lungs in one.

Complications. In three cases the blood sugar was above the normal range noted at this hospital (60 to 120 mg. per cent) but in none of these was diabetes mellitus proved because recorded information was insufficient to rule out glucose infusions as the cause of the hyperglycemia. Other complications included alcoholism in two patients, fatty dystrophy of the liver in one, congestive heart failure in one and osteogenic sarcoma in one. Metastatic abscesses were known to be present in three cases.

Duration of Meningitis from Admission to the Hospital until Death. Among the ten patients who died, the length of the hospital course varied from one to six days and was less than forty-eight hours in six cases. This emphasizes the rapidity of the clinical course from admission to death.

Antibacterial Therapy and Outcome. Four patients received no antimicrobial therapy, four were treated with sulfonamides alone, one received penicillin and streptomycin, and one received the latter two drugs in addition to tetracycline and polymyxin. The only patient

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TABLE I

SUMMARY OF ELEVEN CASES OF KLEBSIELLA MENINGITIS AT PHILADELPHIA GENERAL HOSPITAL

Case (no.)	Year	Age (yr), Sex	Probable Primary Focus	Bacteriologic Data				Duration of Meningitis from Admission to Hospital until Death (days)	Associated Conditions	Antimicrobial Therapy	Result	Remarks
				Cerebrospinal Fluid		Blood Culture	Other					
				Smear	Culture							
1	1936	80, M	Recent trauma to the head	.....	+	..	.....	1	.....	None	Died	.....
2	1936	73, M	Recent trauma to the head	+	Type 2	..	.....	1	Epilepsy, luetic aortitis	None	Died	.....
3	1937	76, F	Otitis media, mastoiditis	.....	Type 2	..	.....	2	Hyperglycemia (250 mg. %)	None	Died	.....
4	1937	43, M	Pneumonia	+	+	+	Kidney	3	Renal abscesses, fatty liver with jaundice	None	Died	.....
5	1938	62, M	Otitis media	.....	+	..	Brain, ear, lung	6	Lung and brain abscess (rt. parietal), hyperglycemia (134 mg. %)	Sulfanilamide	Died	.....
6	1939	43, M	Pneumonia	.....	+	+	Sputum	6	.....	Sulfadiazine	Died	Meningitis developed five days after pneumonia
7	1941	52, M	Otitis media	.....	Type 1	..	.....	1	Congestive heart failure, trauma to the head, alcoholism	Sulfathiazole	Died	Meningitis developed five days after myringotomy
8	1943	40, M	Recent trauma to the head	+	Type 1	..	Kidney, liver	2	Alcoholism, renal and hepatic abscesses	Sulfamerazine	Died	.....
9	1949	46, M	.....	+	Type 1	..	.....	2	Hyperglycemia (222 mg. %)	Penicillin, streptomycin	Died	.....
10	1954	56, M	Urinary tract?	+	Type 8	..	.....	..	Cerebrovascular accident 1 month prior to meningitis	Penicillin, streptomycin, sulfadiazine	Recovered	Meningitis developed five days after trauma to urinary tract
11	1956	35, M	Frontal sinus	Type 2	Type 2	..	.....	1	Osteogenic sarcoma	Penicillin, streptomycin, tetracycline, polymyxin	Died	Meningitis developed five days after hypophysectomy, during which frontal sinus was entered

who recovered was treated with streptomycin, sulfadiazine and penicillin. This patient was infected with klebisella type 8 and there was a possible etiologic relationship to trauma to the lower urinary tract.

It is of interest to note that meningitis in three cases developed while the patient was in the hospital, following known trauma. In each instance the interval between the trauma and onset of meningitis was five days. In two cases the trauma was an operation involving the upper respiratory tract, the presumed origin of the organism. In the other case the patient pulled out his urinary catheter with resultant bleeding, thus providing a portal of entry. The supposition that the urinary tract was the portal of entry in this case is consistent with the fact that the klebsiella was type 8, a type which is commonly found in the urinary tract at this hospital. The five-day interval common to all three cases suggests that the incubation period is of this duration.

Upon analysis of the data on the twenty-one cases [*2–15*] taken from the recent literature (Table II), the following points become manifest. The patients' ages varied from newborn to seventy-three years, and again males predominated (fifteen of eighteen cases). Of ten cases in which the probable primary focus seemed evident, the middle ear was implicated in six, the lower respiratory tract in two, and trauma to the head in two. Klebsiella was cultured from the cerebrospinal fluid in nineteen of the twenty-one

cases and the smear of the cerebrospinal fluid was positive in nine cases. The organism was cultured from the blood in four cases, from the ear in three, arm abscesses in two, sputum in two, and endocardium, urine, spleen and ventricular fluid from single cases. In three of the cases diabetes was an associated condition. Although the duration of the meningitis in the hospital until death was reported to be as long as forty-eight days in one instance, in three of the cases it was less than forty-eight hours. This again emphasizes the severity of the disease and, while eleven of the patients recovered, two of these suffered a residual hydrocephalus.

COMMENTS

The eleven cases reported herein, added to the 119 cases reviewed by Thompson [*1*], and the twenty-one cases reported subsequently [*2–15*], make a total of 151 cases of meningitis due to klebsiella in the literature. Although all of our cases occurred in adults, among the total of 151 cases forty-four were one year of age or less, and sixty-five were ten years old or less. The disease is more common in males than females in a ratio of 5:2.

Clinically, the picture does not differ significantly from other forms of acute meningitis and the cerebrospinal fluid findings are similar. Purpura has been noted in association with klebsiella meningitis [*1*]. Diabetes and debilitating diseases are thought to make the patient more susceptible. *In vitro* studies of klebsiella have shown an increased virulence and greater capsule formation with a glucose concentration of 300 mg. per cent in the media. It has been postulated that an analogous situation may exist *in vivo* in the diabetic subject [*1*].

As has been noted in previous reports [*1*], the most common primary focus of infection is in the upper respiratory tract, followed in descending order by the lower respiratory tract, wound infection, gastrointestinal tract, uterus, genitourinary tract and joints. The findings in the present series of cases are in accord with this.

It can be seen from Tables I and II that in a significant number of cases (fifteen of thirty-two) the organism was identified in the smear of the spinal fluid. In view of the serious prognosis and the rapid clinical course, the finding of a gram-negative encapsulated bacillus morphologically consistent with klebsiella should be followed by vigorous therapy.

Although many of the organisms are capsular types 1 and 2, other types may be involved; for example, type 8 in Case 10 of our series. Revised concepts relating to the taxonomy of klebsiella call for discussion at this point. Extensive studies by Kauffmann [*16*] in Scandinavia and Edwards [*17*] in the United States have indicated the lack of unequivocal morphologic, biochemical or serologic criteria which could serve to distinguish klebsiella from non-motile forms of the organism known as Aerobacter aerogenes. It has therefore been recommended by the investigators cited that both organisms be included in a single genus which, from the standpoint of priority, should be called klebsiella, and that the individual strains within the group, distinguishable by difference in capsular antigens, be differentiated through the use of arabic numerals. By this schema the need for multiple specific names would be obviated. Thus the classic types formerly known as Klebsiella pneumoniae type A through F are now designated as Klebsiella type 1 through 6. To date at least seventy-seven capsular types have been described. These recommendations were adopted in our laboratory in 1952. More detailed discussion of the newer bacteriologic aspects of klebsiella will be found in our previous publications [*18,19*], as well as those of others [*16,17,20*].

At present, the criteria for designating an organism as a klebsiella strain in our laboratory are as follows: A gram-negative, non-motile, aerobic bacillus which ferments lactose, adonitol and inositol, and gives a positive Voges-Proskauer, citrate-utilization and urease reaction, and in addition is indole- and methyl-red-negative. Organisms with this biochemical pattern are then subjected to slide agglutination tests with type-specific capsular antiserums for types 1 to 10 inclusive. If the organism lacks a well defined capsule on primary isolation it is subcultured on media designed to promote the formation of capsules and mucus [*20*]. Strains which fail to agglutinate with available serums are reported as klebsiella species only because a full battery of specific types of serums are not available to us at this time.

Of the eleven cases presented in this report six were either klebsiella type 1 or type 2 and one was type 8. In four cases the type was not recorded. In view of our findings in klebsiella pulmonary disease [*18*] indicating that the classic respiratory types 1 through 4, although less commonly isolated, are more often associated with

TABLE II

SUMMARY OF TWENTY-ONE CASES OF KLEBSIELLA MENINGITIS FROM THE RECENT LITERATURE (1951 TO 1956)

Author and Year of Publication	Case (no.)	Age (yr.), Sex	Probable Primary Focus	Bacteriologic Data				Duration of Meningitis from Admission to Hospital until Death (days)	Associated Conditions	Antimicrobial Therapy	Result	Remarks
				Cerebrospinal Fluid		Blood Culture	Other Cultures					
				Smear	Culture							
Battachary [2], (1951)	..	17, M	.....	..	+	.....	.....	15	.....	Sulfanilamide, penicillin, streptomycin	Died	.....
Evans [3], (1951).....	1	69, M	.....	+	Type 1	.....	Endocardium (type 1), spleen	5	Diabetes, gangrene of toe	Sulfapyridine	Died	.....
	2	46, M	Otitis media	+	Type 1	.....	.....	5	Diabetes	Sulfapyridine	Died	Myringotomy seven weeks prior to admission; mastoidectomy on second hospital day
	3	63, M	.....	+	Type 1	.....	.....	1	Carcinoma ofesophagus	Sulfadiazine	Died	.....
	4	23, M	Otitis media	+	Type 1	.....	Ear (type 1)	.....	Diabetes	Penicillin, sulfadiazine, aureomycin®	Recovered	Acute exacerbation of chronic otitis media two weeks prior to admission
Mossay [4], (1952).....	1	1, ?	Otitis media	+	.....	.....	.....	19	.....	Sulfadiazine, penicillin, streptomycin, soluseptoplyz* (intrathecal)	Died	Meningitis developed four days after acute otitis media
	2	16 days, M	Otitis media	+	+ Diplococcus pneumoniae	.....	Ear, urine, abscess on arm	48	.....	Penicillin, streptomycin	Died	Meningitis developed two weeks after the onset of acute otitis media; postmeningeal hydrocephalus and brachial monoplegia developed
	3	10 days, M	.....	+	+	.....	.....	1	.....	Penicillin, streptomycin, sulfonamide	Died	Convulsions on admission
Trice [5], (1952).....	1	2, F	.....	..	+	+	.....	1 hr, 20 min.	.....	Sulfonamide	Died	Treated for pharyngitis a few hours before meningitis developed
	2	26 days, M	.....	..	+	.....	.....	.....	.....	Penicillin, streptomycin, chloromycetin, varidase®	Recovered	Postmeningeal hydrocephalus developed; died at home five and one-half months after meningitis
Balmes [6], (1953).....	..	11 mo. ?	Upper respiratory infection	..	+	.....	.....	.....	.....	Streptomycin (intramuscular) (intrathecal) sulfadiazine, aureomycin, chloramphenicol	Recovered	Clinical cure of meningitis after three days of streptomycin and sulfadiazine
Blechner [7], (1953).....	1	19 mo., M	.....	+	+	.....	.....	.....	.....	Aureomycin, streptomycin (intramuscular) (intrathecal)	Recovered	Meningitis developed two and one-half weeks after upper respiratory tract infection; treated with penicillin and sulfonamides

TABLE II (*Continued*)

SUMMARY OF TWENTY-ONE CASES OF KLEBSIELLA MENINGITIS FROM THE RECENT LITERATURE (1951 TO 1956)

Author and Year of Publication	Case (no.)	Age (yr.), Sex	Probable Primary Focus	Bacteriologic Data				Duration of Meningitis from Admission to Hospital until Death (days)	Associated Conditions	Antimicrobial Therapy	Result	Remarks
				Cerebrospinal Fluid		Blood Culture	Other Cultures					
				Smear	Culture							
	21	3½, M	.....	+	+	+	.....	.....	.....	Penicillin, aureomycin, streptomycin	Recovered	.....
Eberlie [8], (1953).....	..	5, F	Otitis media	+	+	.....	.....	.....	.....	Penicillin, sulfadiazine, streptomycin (intramuscular) (intrathecal)	Recovered	Meningitis developed eight days after acute otitis media; myringotomy performed
Anderson [9], (1954)....	..	50, M	Pneumonia	..	+	+	Sputum	.....	.....	Penicillin, sulfadiazine, streptomycin (intramuscular), (intrathecal)	Recovered	Meningitis developed six days after pneumonia
Bellora [10], (1954).....	..	Newborn, ?	Trauma to the head	..	+	.....	.....	6	.....	Chloramphenicol	Died	Cyanotic with hemorrhagic spinal fluid at birth; meningitis developed on sixth day
Corcos [11], (1954).....	..	8 mo., M	.....	..	+	.....	.....	.....	Cellulitis of toe	Penicillin, sulfathiazole, streptomycin (intramuscular), (intrathecal), chloramphenicol	Recovered	.....
Steiner [12], (1954).....	..	Newborn, M	Trauma to the head	..	+	.....	.....	.....	.....	Penicillin, streptomycin, chloramphenicol	Recovered	Cyanotic at birth; fever and hemorrhagic spinal fluid noted on sixth day
Montuschi [13], (1954)..	..	48, M	Respiratory tract	..	+	.....	Sputum	.....	.....	Sulfadimidine	Recovered	Meningitis developed ten days after the onset of a cough productive of jelly-like sputum
Bell [14], (1955).....	..	73, F	Otitis media	..	Type 1	Type 1	Mastoid, deltoid abscess	.....	.....	Chloramphenicol, sulfadiazine, streptomycin (intramuscular) (intrathecal)	Recovered	Mastoid and deltoid abscesses incised and drained; chloramphenicol failed to diffuse into spinal fluid in therapeutic concentrations
Corcos, A. [15], (1955)...	..	1, M	.....	..	.....	.....	Ventricular fluid (postmortem)	8	.....	Penicillin, streptomycin, rimifon®	Died	Pseudotetanic crises and opisthotonus two months prior to admission; spinal fluid normal

* Paraminophenylsulfamide; included in Table III in the group treated with sulfonamide-streptomycin and died.

destructive lung disease, the fact that most of the typed strains in our cases of meningitis were types 1 and 2 suggests that these types are apt to be more virulent than higher types. At this institution type 8 is more commonly found in the urinary tract than in the respiratory tract; this is consistent with the suspicion that the portal of entry in the patient whose meningitis was due to type 8 was the lower urinary tract.

Susceptibility studies in our laboratory [*19*] indicate that klebsiella organisms isolated from a variety of sources show the highest incidence of susceptibility to chloramphenicol. In order of diminishing activity, the other agents were oxytetracycline, streptomycin and chlortetracycline. In a later study [*18*], limited to strains isolated from the respiratory tract, 81 per cent of the strains tested were susceptible to chloramphenicol, 74 per cent were susceptible to streptomycin, and 63 per cent were susceptible to tetracycline.

On the basis of *in vitro* studies, therefore, chloramphenicol and streptomycin would appear to be the drugs of choice. However, in the treatment of meningitis streptomycin leaves something to be desired because it does not diffuse freely into the cerebrospinal fluid [*14*], and intrathecal streptomycin is apt to produce untoward effects. This does not pertain to the same degree in the case of sulfonamides and chloramphenicol. Chloramphenicol yields higher spinal fluid concentrations than the tetracyclines (chlortetracycline and oxytetracycline) and has been reported to occur in concentrations of from 30 to 50 per cent of the levels found in the blood [*14*]. However, a word of caution is indicated because Bell [*14*] reported a patient who recovered despite the fact that, although chloramphenicol blood levels were high, chloramphenicol did not reach the spinal fluid in therapeutic concentrations. This patient was also treated with sulfadiazine and streptomycin.

Sulfadiazine diffuses into the spinal fluid at levels of 50 to 70 per cent of blood levels when parenterally administered [*14*]. This drug has been found effective in experimental infections due to K. pneumoniae in mice [*14*]. On the basis of the foregoing information it would appear that sulfonamides and chloramphenicol are the antimicrobials of choice for the treatment of klebsiella meningitis. While the clinical efficacy of sulfonamides is borne out by a review of the results of therapy culled from the literature and in our own series, the evidence for chloramphenicol is equivocal, due to the small number of patients treated with this agent.

Table III summarizes the results of the various forms of treatment used. While many of the patients received penicillin in addition to other drugs, this antibiotic was not included in the analysis because penicillin in the dosages employed is believed to have little or no effect against klebsiella. The sulfonamides offered the first effective weapon in klebsiella meningitis. Prior to their use, recovery was rare. The number of patients treated with streptomycin alone is small, but all the patients died, which suggests that this antibiotic is ineffective. In contrast, although the number of cases again is small, patients treated with broad-spectrum antibiotics in addition to other agents have usually recovered. No definite conclusions are warranted because some of these patients also received sulfonamides. Only five patients have received chloramphenicol with other drugs and four of these recovered.

TABLE III
SUMMARY OF THERAPY AND RESULTS IN 151 CASES OF KLEBSIELLA MENINGITIS

Therapy	Number Died	Number Recovered
None	61	4
Sulfonamide	25	19
Streptomycin	6	0
Sulfonamide-streptomycin	13	11
Broad spectrum	1	0
Broad spectrum-sulfonamide	0	1
Broad spectrum-streptomycin	0	5
Broad spectrum-streptomycin-sulfonamide	0	4
Broad spectrum-streptomycin-polymyxin	1	0
Total	107	44

SUMMARY

Eleven cases of klebsiella meningitis are added to the 140 cases reported in the literature. These cases are discussed in relation to clinical features, the capsular serotype of the organism and antimicrobial therapy.

The disease is often fulminating. Most cases have occurred in adults. Meningitis is usually secondary to klebsiella infection of the respiratory tract, is most commonly due to types 1 and 2, and sometimes follows trauma to the head. Diabetes and debilitating diseases seem to be predisposing factors. Metastatic abscesses are frequent.

A case of infection with klebsiella type 8 is reported. Recent bacteriologic developments with respect to klebsiella serotypes are discussed.

The available information to date suggests that the drugs of choice are the sulfonamides. The status of the broad-spectrum agents, although promising, is equivocal because of the relatively few cases in which they have been used. In view of the serious nature of this form of meningitis it is recommended that both sulfonamides and broad-spectrum antibiotics be administered at once when a gram-negative encapsulated bacillus is found in the spinal fluid.

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Fungus Infections Associated with Antibiotic and Steroid Therapy*

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WITH increase in the use of antibiotic and steroid therapy there has been a growing awareness of complicating "lower form" infections, notably those due to fungi. Although such organisms may in part represent normal microbial human flora, they have posed few problems of pathogenesis in the past except in isolated debilitating disease states. Following antibiotic and steroid therapy some change is presumed to occur, either in the infecting agent or in the host, to enhance the growth of these agents and to predispose to active infection. This contribution is intended to shed some light on the nature of these changes and to determine whether or not such fungus infections represent a hazard sufficient to suggest revision of present concepts of combined antibiotic and steroid therapy.

Most prominent among the fungus infections are those due to Candida albicans. An increased incidence of cultures positive for monilia, notably from the gastrointestinal tract, has been reported often, even after only five days of antibiotic therapy [*1–3*]. Disseminated monilial infestations which probably influenced patient mortality have also been described [*4–7*]. A serious objection to this interpretation, however, has been raised by Kligman [*8*] who doubts the clinical importance of complicating fungus infection. Recently, however, Wolf [*9*] reported a patient with pneumonia whose sputums showed a change in infective flora from bacteria to fungi while under antibiotic therapy. Cessation of antibiotic therapy was followed by striking clinical improvement. Moniliasis has also been reported in association with steroid therapy by Shulman [*10*] and Levy [*11*], but Benedek [*12*] denies such clinical correlation. In addition, other fungi such as aspergillus [*13*] and mucor [*14,15*], have been identified as causative agents in disseminated infections.

At Montefiore Hospital an increase in fungus infestation has been observed at necropsy in recent years. Thirteen cases of such fungus infection have occurred in the past three years, ten in the past year. These cases will be summarized and details will be given of the antibiotic steroid or other specific therapy. A word concerning identification of the fungi in these cases is necessary. In only one instance was there clinical suspicion of infection before death and a positive culture for monilia was obtained from the mouth. In the remaining cases no cultures were obtained and the diagnosis was made from the presence of mycelia and yeasts in microscopic preparations. Mycelia were identified in all instances. Hyphae which are relatively narrow in width (4 microns), often club-shaped and septate, and have prominent blastospores, are considered compatible with the morphology of C. albicans. (Fig. 1.) Hyphae which are of medium width (15 microns), often septate and display prominent branching, are probably those of aspergillus. (Fig. 2.) Hyphae which have distinct irregularity in width (6 to 50 microns), are non-septate and coenocytic, and have marked lateral branching, are considered to be mucor. (Fig. 3.) These criteria may be accepted for identification only in the absence of cultures which are more specific and accurate. With these limitations in mind the following cases are presented.

CASE REPORTS

CASE I. (M. H. 64889) This was the second Montefiore Hospital admission of a fifty-seven year old white woman who had had a left radical mastectomy for anaplastic carcinoma of the breast six months prior to admission. She had been given postoperative radiotherapy but this had to be discontinued because of the onset of leukopenia, which persisted to the time of admission. Physical examination revealed striking

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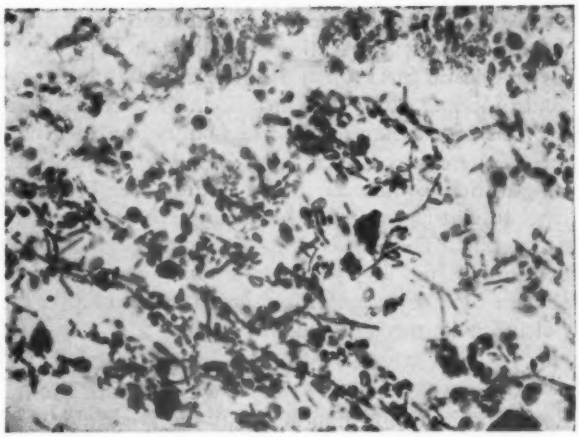

FIG. 1. Small, club-shaped, septate hyphae containing blastospores. These hyphae are morphologically compatible with Candida albicans; original magnification, × 440.

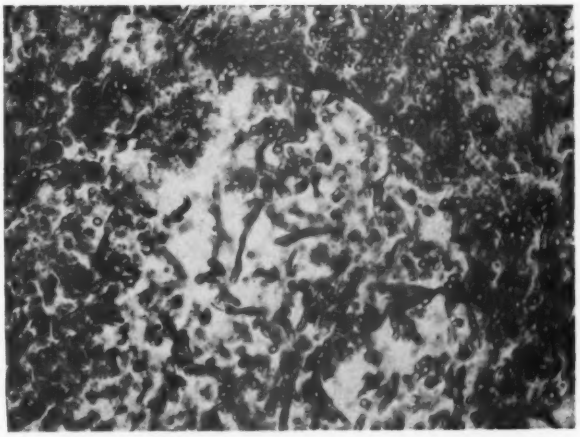

FIG. 2. Photomicrograph of septate, spore-bearing hyphae of medium size with prominent branching, consistent with aspergillus; original magnification, × 440.

pallor, the scar of a left radical mastectomy, and edema of the left arm. The hematocrit was 33 per cent on admission and approximately 27 per cent thereafter. The white blood cell count was 2,000 per cu. mm. with 80 per cent of lymphocytes on admission. Leukocytes thereafter ranged from 500 to 1,300 cells per cu. mm. with 90 per cent lymphocytes. During her third month in the hospital stomatitis developed and a culture revealed C. albicans. After antibiotic therapy for four months and steroid therapy for two months, the patient died on the 131 hospital day.

Necropsy revealed a well developed, well nourished woman with no residual evidence of carcinoma. The bone marrow was normoplastic with almost complete absence of mature forms of the myeloid series. Grossly the lung was normal but in microscopic preparations granulomatous lesions with centers of coagulative necrosis were found. In the peripheral cellular zones, numerous medium-sized septate hyphae were seen with prominent branching, morphologically consistent with aspergillus. There were multiple ulcerations in the mucosa of the epiglottis, pharynx and esophagus. These ulcers contained septate, club-shaped, small hyphae similar to monilia. The hyphae did not penetrate into the deeper layers of these structures.

CASE II. (M. H. 72207) This was the second Montefiore Hospital admission of the forty-five year old white man who was found to have Hodgkin's disease (cervical biopsy) two and a half years prior to admission. Three months prior to admission pancytopenia was noted; this was treated with transfusions and cortisone (60 mg. every other day), until his hospitalization because of weakness and fatigue. Physical examination revealed marked pallor of the skin and mucous membranes, hemorrhages in the ocular fundi, palpable liver and spleen, and rubbery axillary lymph nodes. The hematocrit was 11 per cent on admission and ranged from 13 to 33 per cent afterwards. The

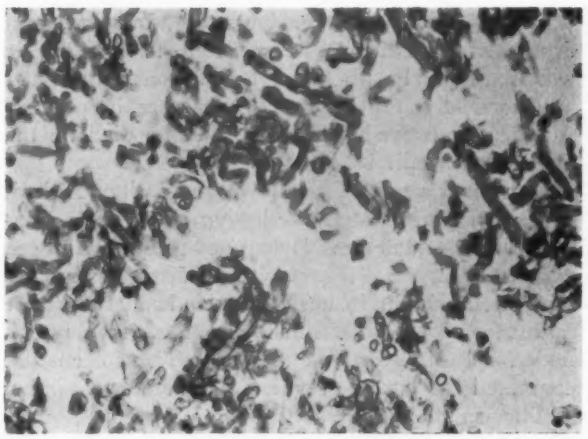

FIG. 3. Large, irregular, non-septate, spore-bearing hyphae with lateral branching. These hyphae are consistent with mucor; original magnification, × 440.

white blood cell count was 2,750 cells per cu. mm. on admission and varied from 2,500 to 4,500 cells per cu. mm. afterward. Blood platelets were diminished. He was maintained with blood transfusions and cortical steroids throughout hospitalization, and antibiotics during the last four weeks of hospitalization. His second month in the hospital was characterized by remission but thereafter his condition rapidly deteriorated; he became icteric terminally and died on the 106 hospital day.

Necropsy revealed a well developed white man with hepatomegaly (2,650 gm.) and splenomegaly (835 gm.), generalized lymphadenopathy and multiple gastric erosions. Microscopically there were infiltrates of Hodgkin's lymphoma in the lymph nodes, spleen, liver and bone marrow. There was an area of coagulative necrosis in the lungs with overgrowth of medium-sized, septate hyphae, with prominent branching, which resembled aspergillus. The erosions of the gastric mucosa had a necrotic base containing small

septate, club-shaped hyphae with prominent blastospores which resembled monilia. These latter fungi did not penetrate into the deeper layers of the gastric wall.

CASE III. (M. H. 57722) This was the first Montefiore Hospital admission of a five year old white boy of Puerto Rican extraction. At the age of two and a half years acute leukemia had developed, and he now entered the hospital because of an acute exacerbation of leukemia. This constituted the fourth documented exacerbation, and each episode had been effectively treated with blood transfusions, ACTH, cortisone and penicillin. Physical examination revealed cervical and inguinal lymphadenopathy, palpable liver and spleen, and a diffuse pharyngitis. The white blood cell count was 166,400 cells per cu. mm. on admission with 98 per cent mononuclear forms. The leukocyte count progressively dropped to 2,000 cells per cu. mm. terminally. The platelet count was 78,000 cells per cu. mm. on admission, and dropped to 10,000 cells per cu. mm. terminally. He was maintained with blood transfusions, antibiotics and cortical steroids throughout his hospital course. All therapy proved ineffectual, and he died on the forty-ninth hospital day.

Necropsy revealed a well developed, well nourished, white boy with enlarged fleshy lymph nodes and enlarged liver (1,250 gm. Normal 600 gm.). The spleen was also enlarged (215 gm. Normal 50 gm.) and contained yellowish infiltrates. Microscopically there were infiltrates of myeloblasts in the bone marrow, lymph nodes, spleen, liver and stomach. The spleen also contained a focus of coagulative necrosis containing septate, small hyphae, with prominent blastospores. These fungi morphologically resembled monilia.

CASE IV. (M. H. 74754) This was the first Montefiore Hospital admission of a sixty-five year old white man who was found to have a carcinoma of the bladder one month prior to admission. The tumor was deemed inoperable and he was admitted for radiotherapy. Physical examination revealed a suprapubic cystostomy and compression of the rectal lumen anteriorly by an extrinsic tumor mass. The hematocrit was 32 per cent on admission and dropped to 20 per cent terminally. The white blood cell count was 6,400 cells per cu. mm. on admission with a normal differential count, and the count ranged from 4,000 to 24,000 thereafter. The serum acid phosphatase ranged from 5.5 to 15.2 King-Armstrong units (normal up to 3.0 units). Persistent urinary tract infection developed for which he received antibiotic therapy for twelve weeks. The tumor mass obstructed the ureters and rectum; to relieve this obstruction ureterostomy and colostomy were performed. He died four months after admission.

Necropsy revealed a tumor invading the bladder, prostate and rectum; bilateral pyelonephritis; a metastatic lesion in the liver, and aspiration pneumonia. Microscopic section revealed the tumor to be an anaplastic carcinoma. The lungs had an extensive acute inflammatory infiltrate in the alveolar spaces, necrosis of alveolar septa, and many clumps of bacteria. There was also an area of suppuration in the lung which contained many medium-sized, septate hyphae, with prominent branching; these resembled aspergillus. The stomach had a mucosal ulceration containing budding yeasts and small, septate, club-shaped hyphae resembling monilia. The monilia did not infiltrate the stomach wall.

CASE V. (M. H. 41734) This was the sixth Montefiore Hospital admission of a sixty-four year old white man in whom a diagnosis of reticulum cell sarcoma had been made ten years prior to admission. He entered the hospital because of abdominal distention of one month's duration. Physical examination revealed abdominal distention, ascites and a palpable mass in the right upper quadrant of the abdomen. Laboratory data revealed a hemoglobin of 11.5 gm. per cent on admission with no significant change throughout hospitalization. The white blood cell count was 4,200 cells per cu. mm. on admission, with subsequent counts ranging from 3,300 to 6,000 cells per cu. mm. He was treated with radiation and paracenteses for recurrent ascites. He received antibiotic therapy for thirty-one days and steroid therapy for one week. Respiratory distress developed terminally and the patient died on the seventy-eighth hospital day.

Necropsy revealed a well developed, well nourished, white man with 2,000 cc. of serous fluid in each pleural cavity and 4,000 cc. of serous ascitic fluid. All serous membranes were thickened by fibrous tissue and inflammatory exudate. The mass in the right upper quadrant was composed of a thickened gallbladder and dense fibrous adhesions between the small intestine and transverse colon. There were multiple erosions on the gastric mucosa. Microscopic preparations revealed infiltration of malignant lymphocytes in lymph nodes, bone marrow, spleen, liver, pleura, peritoneum and mesentery. The gastric ulcers contained numerous small, septate, club-shaped hyphae with prominent blastopores. These hyphae resembled monilia. They did not infiltrate the deeper layers of the stomach wall.

CASE VI. (M. H. 53008) This was the first Montefiore Hospital admission of a fifty-nine year old white woman in whom a diagnosis of reticulum cell sarcoma of the jejunum had been made six months prior to admission. She was admitted for palliative radiotherapy. Physical examination revealed a large palpable mass in the right upper quadrant, and marked edema of the lower extremities. The hemoglobin was 11.5 gm. per cent on admission and the white blood cell count was 12,800 cells per cu. mm.

with 82 per cent polymorphonuclear leukocytes. Five days after admission abdominal distention and shock occurred. Therapy included tube-decompression of the bowel and antibiotic therapy of five days' duration. She died on the eleventh hospital day.

Necropsy revealed a well developed, poorly nourished, white woman with recurrence of tumor at the site of a previous jejunal anastomosis. She also had constriction of the intestinal lumen, perforation of the bowel wall and fecal peritonitis. There was a gangrenous necrosis of the mucosa of the distal esophagus. Microscopic preparations disclosed reticulum cell sarcoma at the site of perforation of the bowel, and an acute inflammatory exudate on the peritoneal surfaces. All layers of the esophagus displayed widespread degenerative change with mucosal ulceration. The ulcers contained a necrotic base with numerous small, septate hyphae having prominent blastospores. These fungi resembled monilia and were confined to the surfaces of the ulcers.

Case vii. (M. H. 68397) This was the fourth Montefiore Hospital admission of a sixty-four year old white man in whom a diagnosis of multiple myeloma had been made one and a half years prior to admission. During the patient's third hospitalization, which was seven months prior to this admission, hemolytic anemia developed and corticosteroid and antibiotic therapy was initiated. This was continued until he died eight months later. This last admission was occasioned by the onset of epigastric pain and vomiting. Physical examination revealed a mild icterus, basilar pulmonary rales, hepatomegaly and rebound abdominal tenderness in the right lower quadrant. Throughout hospitalization the white blood cell count ranged from 4,100 to 8,700 cells per cu. mm. and the hemoglobin from 6.5 to 8.5 gm. per cent. He became increasingly azotemic, his blood urea nitrogen rising to 90 mg. per cent terminally. He died on the twentieth hospital day.

Necropsy revealed a well developed, well nourished white man. The heart weighted 510 gm. and was concentrically hypertrophied. The myocardium had a focus of hemorrhagic discoloration in the left ventricle. The liver weighed 1,560 gm., was soft in consistency and yellow-brown. The spleen weighed 530 gm. and was soft. The bone marrow appeared of soupy consistency and was reddish brown. Microscopically there were infiltrates of myeloma cells in the bone marrow, liver, spleen and lymph nodes. The liver was almost completely necrotic and, in addition, had myeloma infiltrates. There was a focal endocarditis of the left auricle and ventricle with overgrowth of large, non-septate hyphae with lateral branching. The organisms resembled mucor. There was a thrombus in a coronary vessel containing similar fungi. The vessel was surrounded by a hemorrhagic myocardial infarct. Similar thrombi were found in pulmonary, splenic, gastric and meningeal vessels. There was focal ulceration of the gastric mucosa. A suppurative meningitis was present which was due to the same fungus.

Case viii. (M. H. 73871) This was the second Montefiore Hospital admission of a sixty-three year old white woman. Carcinoma of the ovary had been diagnosed two years prior to admission. She had had a left radical mastectomy because of carcinoma of the breast twenty years prior to admission, with no apparent recurrence of this tumor. The last admission was prompted by the development of urinary tract infection and recurrent ascites. Physical examination revealed a left mastectomy scar, cardiomegaly, abdominal distention, hepatomegaly, a large pelvic mass, and marked edema of both lower extremities. The hemoglobin was 12.0 gm. per cent on admission and dropped to 5.0 gm. per cent terminally. The white blood cell count varied from 5,300 to 3,300 cells per cu. mm. with a normal differential count. She had persistent albuminuria and mild azotemia developed terminally. The patient became febrile following paracentesis and antibiotics were administered for twenty days. She became progressively debilitated, and died on the thirty-third hospital day.

Necropsy disclosed a well developed, poorly nourished white woman. On opening the abdomen 1,500 cc. of cloudy, hemorrhagic ascitic fluid was found, and the peritoneal surfaces were coated with a mottled pale green inflammatory exudate. There was a partially necrotic pelvic tumor mass, bilateral hydronephrosis, and numerous intestinal fibrous adhesions. The esophagus had mucosal ulcerations and tumor nodules embedded in the wall. Microscopic study revealed the tumor mass to be a papillary adenocarcinoma. The esophageal mucosa was focally ulcerated and covered with a necrotic exudate in which were seen aggregates of small, club-shaped, septate hyphae having prominent blastospores. These fungi resembled monilia. Numerous budding yeasts resembling monila were also present. There was no infiltration of these organisms into the deeper layers of the esophageal wall. There was also an aspiration pneumonia, in which bacteria and budding yeasts were prominent.

Case ix. (M. H. 77589) This was the first Montefiore Hospital admission of a seventy-three year old white woman who was admitted because of weakness and anorexia of three months' duration. The patient had been known to have hypertension for many years, anemia for at least two years, and arthritic joint pain for two years. She had a course of cortisone therapy for three months, ending three months prior to admission. Physical examination revealed a blood pressure of 210/110, marked pallor of the skin and mucous membranes, mild cardiomegaly and slight peripheral edema. During hospitalization the hematocrit ranged from 20 to 27 per cent, the white blood cell count

ranged from 7,600 to 13,900 cells per cu. mm., and the blood urea nitrogen ranged from 100 to 155 mg. per cent. The patient was believed to have uremia secondary to nephrosclerosis. Pyelonephritis developed, for which antibiotic therapy was administered for twenty-seven days. No significant response was obtained and she died on the twenty-eighth hospital day.

Necropsy revealed a well developed, well nourished white woman with marked edema of the lower extremities. The right kidney weighed 95 gm. and the left 90 gm., each having marked narrowing of the cortex and reddish white mottled discolorations. The lower half of the esophagus had a necrotic, ulcerated mucosa. Microscopic preparations of the kidney disclosed arteriosclerosis and arteriolosclerosis, interstitial fibrosis and necrotizing arteritis. There was also a necrotizing arteritis in the pancreas, spleen, skeletal muscle, gastrointestinal tract, ovaries and urinary bladder. The esophagus presented a focally ulcerated mucosa, with an overlying necrotic exudate in which there were abundant small, club-shaped, septate hyphae with blastospores. These resembled monilia. There were also numerous yeast cells and polymorphonuclear leukocytes in the exudate.

Case x. (M. H. 73617) This was the second Montefiore Hospital admission of a sixty-five year old white man who had had aplastic anemia for two years. His pancytopenia was treated with blood transfusions, vitamin B_{12}, ACTH and cortisone with little or no significant response. Physical examination on admission revealed a pallid white man with flame-shaped hemorrhages in both ocular fundi, and dried blood in his nostrils. The laboratory findings included a hematocrit which ranged from 9 to 16 per cent and a white blood cell count which ranged from 350 to 1,200 cells per cu. mm., with lymphocytes chiefly present. Platelets were persistently diminished in peripheral blood smears. Cortical steroid therapy was given for thirty-three days, and antibiotic therapy for thirty-one days. On the day prior to death the patient had a bloodstained bowel movement. He died on the thirty-fourth hospital day.

Necropsy revealed a poorly nourished white man with purpuric skin lesions on all four extremities. The spleen weighed 335 gm. and was congested. There was a hemorrhagic focus in the gastric mucosa measuring 1 by 2 cm. A segment of small intestine, approximately 10 feet in length, was filled with clotted blood. The mucosa in this portion of the intestine was hemorrhagic and was covered by a dirty, necrotic membrane. Grossly, the bone marrow was normal. Microscopically, the bone marrow was normoplastic but virtually all marrow cells were immature forms. The mucosa of the small intestine was hemorrhagic, focally ulcerated, and covered by a necrotic exudate containing large islands of Gram-positive cocci. The gastric mucosa had a focal ulceration overlying thrombosed submucosal blood vessels. The thrombi contained masses of non-septate, coenocytic hyphae of markedly irregular width and with prominent lateral branches. These hyphae were morphologically consistent with mucor.

Case xi. (M. H. 77651) This was the second Montefiore Hospital admission of a fifty year old white woman in whom a diagnosis of plasma cell leukemia had been made one month prior to admission. She had received urethane (3 gm. daily) and meticorten since her previous discharge from the hospital. She was readmitted because of pneumonia of one day's duration. Physical examination revealed petechiae over the chest, a left pleural friction rub and a palpable liver and spleen. The white blood cell count was 5,400 cells per cu. mm. with 75 per cent plasmacytes. The hematocrit was 24 per cent. Urethane was stopped on the fifth hospital day. She was given antibiotic therapy for two weeks and cortical steroids throughout hospitalization. All therapy was to no avail; a hemorrhage occurred from the mucous membranes and the patient died on the seventeenth hospital day.

Necropsy showed a poorly nourished white woman with petechiae in the skin over the chest. The liver weighed 1,900 gm. It was yellow-tan and contained numerous reddish white infiltrates. The spleen weighed 925 gm. and had a flesh-colored surface on section. There was generalized lymphadenopathy. The bone marrow was pale red. There was an antemortem clot in the left pulmonary artery and a hemorrhagic infarct in the left lung. Microscopic preparations revealed an infiltration of plasma cells in the liver, spleen, bone marrow, lymph nodes, kidneys and stomach. The pulmonary artery was occluded by a thrombus which contained numerous large, non-septate, coenocytic hyphae, morphologically similar to mucor. There was a hemorrhagic infarct in the lung, containing numerous similar but partially necrotic fungi.

Case xii. (M. H. 41643) This was the fourth Montefiore Hospital admission of a sixty-three year old white woman. Carcinoma of the esophagus had been discovered one week prior to admission. Physical examination at the time of admission was unrevealing. The white blood cell count throughout hospitalization averaged approximately 10,000 cells per cu. mm. with a preponderance of polymorphonuclear leukocytes. The hematocrit averaged about 35 per cent. The patient refused surgical resection and instead received a course of radiotherapy. Neoplastic obstruction developed in the esophagus and trachea, for which palliative gastrotomy and tracheotomy were performed. The last four months of hospitalization were marked by recurrent urinary tract infection for which antibiotic therapy was administered for sixty-two days. She died approximately one year after admission.

Necropsy disclosed an emaciated white woman with patent tracheostomy and gastrostomy wounds. A tumor mass was found in the neck infiltrating and occluding the esophagus, larynx and trachea. Microscopic preparations revealed the tumor to be a squamous cell carcinoma. There was erosion of the esophageal mucosa overlying the tumor with a base of necrotic cellular debris. There were numerous small, club-shaped, septate hyphae with prominent blastospores in the necrotic debris. Some yeast cells were seen. These fungi and yeasts were morphologically compatible with monilia. They did not infiltrate the esophageal wall.

CASE XIII. (M. H. 68841) This was the first Montefiore Hospital admission of a fifty-eight year old white man in whom a diagnosis of polycythemia vera was made nine months prior to admission. He was transferred to this hospital because of weakness following hemorrhage. Physical examination revealed an emaciated man with infected decubiti and sensory disturbances in the upper and lower extremities. His red blood cell count ranged from 7,900,000 to 3,200,000 cell per cu. mm.; the white blood cell count from 24,000 to 172,000 cells per cu. mm.; the platelet count from 128,000 to 780,000 cells per cu. mm. Initially he was treated with radiation, which was discontinued because of a rapidly rising white blood cell count. Following this, a course of myleran® therapy was given for nine months. This had no distinct effect and was discontinued four months prior to the patient's death. Six months prior to death persistent pyuria developed for which antibiotic therapy was given for five months. Terminally, a massive gastrointestinal hemorrhage occurred, he became icteric, and died. No antibiotic therapy was used during the last two weeks except for achromycin,® which was administered on the last two hospital days.

Necropsy revealed a poorly nourished, emaciated white man with 800 cc. of serous ascitic fluid. There was an operative absence of the spleen. The liver weighed 1,650 gm. and was golden yellow. There were vegetative lesions on the mitral valve. A mucosal ulceration was seen in the stomach, and the duodenum contained two large ulcer craters. Microscopic preparations revealed a hypercellular bone marrow, with erythroid and myeloid hyperplasia. The liver contained many foci of necrosis, and there were infiltrates of nucleated red cells and lymphocytes. The vegetations on the mitral valve contained fibrin, a few inflammatory cells but no bacteria. The ulcers in the stomach and duodenum had a necrotic base in which there were numerous budding yeasts and hyphae. The latter were small, septate, club-shaped and had prominent blastospores. They did not invade the deeper layers of the stomach or duodenal wall.

RESULTS

There was no age, sex or race predilection in this series of cases. Diabetes was not present in any patient, although diabetes is recognized as an important predisposing factor. In eight instances a disorder of the hemapoietic system was the basic disease; this is in conformity with the recognized association of lymphoma and fungus disease. Leukopenia was present in only five cases but in five others there was an associated blood dyscrasia. Virtually all clinically tested antibiotics, except aureomycin, were involved. (Table I.) Aureomycin, incidentally, has been one of the chief antibiotics implicated in the pathogenesis of experimental fungus infection. All commonly used cortical steroids were implicated.

In analyzing the pathologic lesions two basic characteristics of infection were recognized. In one group the fungus growth appeared to be confined to the surface of mucous membranes, with no infiltration of deeper tissues. (Fig. 4.) This group comprised five cases (Cases VI, VIII, IX, XII and XIII). The duration of antibiotic therapy in these cases ranged from five days to a year. Steroid therapy was not given in four cases and in the fifth steroids were stopped four months prior to death. In case XIII the patient received prolonged antibiotic therapy for one and a half years but had received no steroids. The second group comprised lesions which can be considered to be invasive. (Fig. 5.) This group comprised eight cases (Cases I, II, III, IV, V, VII, X and XI). The duration of antibiotic therapy ranged from two weeks to nine months. In this group, however, only one person received no steroid therapy. The remaining seven received steroids for one week to eight and a half months.

Table II presents the frequency of organ involvement and the type of infecting organism. As is seen, monilia was the most frequent fungus found. On three occasions monilial gastrointestinal lesions were associated with aspergillus in the lung. Aspergillus and mucor were each present three times. In two instances (Cases VI and XI) the fungi were believed to be the direct cause of death. In at least five patients (Cases I, II, III, IV and X) the fungi were believed to contribute significantly to the patients' death. The fungi seemed to present only a potential hazard in the remaining cases.

COMMENTS

The cases reported in this communication emphasize the need for discretion in the combined use of antibiotic and steroid therapy. Many experiments have been reported which

TABLE I

DOSAGE OF COMBINED ANTIBIOTIC AND STEROID THERAPY

Drug		Case												
		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Penicillin (million units)	Dosage	1.2	1.2	0.6	1.2	0.6–1.2	0.5	1.2	0.6	.....	1.2	.....	0.6	.....
	Days	24	23	10	50	31	5	24	20	.....	26	.....	3	.....
Streptomycin (gm.)	Dosage	1.0	1.0	1.0	1.0	1.0	2.0	1.0	1.0	0.5	.....	.....	1.0	1.0
	Days	39	23	18	50	9	5	21	20	1	.....	.....	3	30
Terramycin® (gm.)	Dosage	.....	.....	1.0	.....	.....	...	.....	...	.....	.....	.....	0.3	1.0
	Days	.....	.....	29	.....	.....	...	.....	...	.....	.....	.....	3	14
Chloromycetin (gm.)	Dosage	.....	.....	2.0	0.3–2.0	.....	...	.....	...	.....	.....	.....	.....	0.5–1.0
	Days	.....	.....	9	45	.....	...	.....	...	.....	.....	.....	.....	39
Gantrisin® (gm.)	Dosage	.....	.....	.....	4.0	.....	...	.....	...	2.0–4.0	.....	.....	2.0–4.0	4.0
	Days	.....	.....	.....	5	.....	...	.....	...	18	.....	.....	40	48
Furadantin® (mg.)	Dosage	.....	.....	.....	.....	.....	...	.....	...	400	.....	.....	300	400
	Days	.....	.....	.....	.....	.....	...	.....	...	9	.....	.....	16	302
Mycostatin® (million units)	Dosage	1.4	.....	.....	.....	.....	...	.....	...	.....	.....	.....	.....	.....
	Days	36	.....	.....	.....	.....	...	.....	...	.....	.....	.....	.....	.....
Tetracycline (gm.)	Dosage	1.0	.....	.....	.....	.....	...	.....	...	1.3	0.75	1.0	.....	1.0
	Days	71	.....	.....	.....	.....	...	.....	...	5	5	13	.....	2
Erythromycin (gm.)	Dosage	1.2	.....	.....	0.4–0.8	.....	...	.....	...	.....	.....	.....	.....	1.0
	Days	31	.....	.....	7	.....	...	.....	...	.....	.....	.....	.....	47
Neomycin (gm.)	Dosage	.....	.....	.....	2.0	.....	...	.....	...	.....	.....	.....	.....	800
	Days	.....	.....	.....	5	.....	...	.....	...	.....	.....	.....	.....	22
Cortisone (mg.)	Dosage	75–300	.....	50–100	.....	40–80	...	.....	...	.....	200–400	.....	.....	.....
	Days	65	.....	21	.....	2	...	.....	...	.....	33	.....	.....	.....
ACTH (units)	Dosage	.....	10–90	20–80	.....	80	...	10–80	...	.....	90	.....	.....	.....
	Days	.....	75	23	.....	2	...	157	...	.....	5	.....	.....	.....
Corticotropin (units)	Dosage	.....	.....	80	.....	.....	...	.....	...	.....	.....	.....	.....	.....
	Days	.....	.....	3	.....	.....	...	.....	...	.....	.....	.....	.....	.....
Prednisone (mg.)	Dosage	.....	20–40	.....	.....	.....	...	20–40	...	.....	.....	25–100	.....	.....
	Days	.....	22	.....	.....	.....	...	81	...	.....	.....	45	.....	.....
Hydrocortisone (mg.)	Dosage	.....	100–200	.....	.....	100	...	.....	...	.....	.....	.....	.....	.....
	Days	.....	76	.....	.....	5	...	.....	...	.....	.....	.....	.....	.....

leave small doubt as to the influence of antibiotics on infection by fungi. They may affect the organisms or the host, or both. They may promote both the growth and virulence of the infecting agents.

Virtually all antibiotics have been associated with fungus infections. However, *in vitro* stimulation of monilial growth has been demonstrated only for aureomycin, bacitracin and neomycin [*16,17*]. Seligman [*18,19*] has reported increased virulence in mice treated with aureomycin and terramycin. Hazen et al. [*20*] have confirmed these results but Munoz et al. [*21*], De Mello et al. [*22*], and Dukes and Tettelbaum [*23*] disagree with these conclusions. Some of the possible mechanisms of host influence are alterations of the immunologic response, alteration of the gastrointestinal flora, or direct tissue toxicity. Stevens [*24*] and Shanetz [*25*] have reported evidence to indicate depression of antibody titers in laboratory animals following prolonged feeding of antibiotics. However, feeding for brief periods appeared to increase the titers. Allen [*26*] disagreed with this view entirely, stating that since he found no difference in survival time there could be no significant effect on antibody titers. Much of the evidence of fungus stimulation is based on the increased occurrence of fungi in the gastrointestinal tract, where they are normal inhabitants.

It is known that temporary quantitative depression of the bacterial flora occurs and that this depression chiefly involves gram-positive organisms [*27,28*]. It is presumed that this reduc-

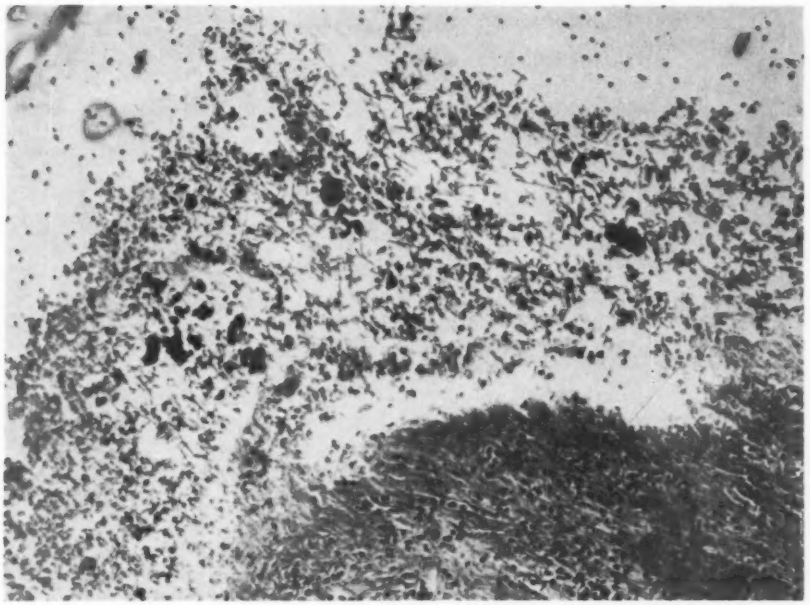

FIG. 4. Surface proliferation of fungi in esophagus. The hyphae are admixed with necrotic debris and yeast cells. Note the esophageal musculature in the lower right side of figure; original magnification, × 150.

tion of bacterial forms allows "saprophytic" fungi to proliferate [*29*].

In regard to direct tissue toxicity, it has long been recognized that aureomycin is irritating when injected intraperitoneally, intramuscularly, subcutaneously or intracutaneously [*30*]. Dukes and Tettlebaum [*23*] have shown that potentiation of fungus infection occurs only when the same route of entry is used for antibiotic and fungus. De Mello [*22*], moreover, has demonstrated the occurrence of fungus potentiation with aureomycin derivatives which possess no antimicrobial activity. Thus, although there are many contradictory data, there appears to be some correlation between antibiotic therapy and fungus growth. Reduction of competitive flora and irritative tissue injury appear to represent the best explanation for the mechanism of the infections.

The effects of cortical steroids on infection are even more difficult to explain. They have long been implicated in chronic inflammatory responses and fibroblastic proliferation in particular. However, they also appear to be involved in acute inflammatory and immunologic responses. All these mechanisms may play a role in complicating fungus infection.

In regard to the acute inflammatory response, there appears to be a definite alteration of leukocytic activity. This effect may be direct or indirect. Several investigators have reported a diminution in onset, intensity and duration of endothelial sticking of leukocytes [*31–33*]. Crepea et al. [*34*] and von Moeschlin [*35*] have shown diminished phagocytosis. Lurie et al. [*36*] have demonstrated increased phagocytosis but diminished digestion of phagocytosed material.

TABLE II
FREQUENCY OF ORGAN INVOLVEMENT WITH FUNGI

Organs Involved	No. of Cases	Fungi		
		Monilia	Mucor	Aspergillus
Stomach	6	4	2	..
Lung	5	..	2	3
Esophagus	5	5	..	..
Spleen	2	1	1	..
Heart	1	..	1	..
Kidney	1	..	1	..
Brain	1	..	1	..

The effect on the leukocyte may also be indirect. There is a known vascular effect, namely, increased arteriolar tone producing diminished blood flow, hemorrhage and edema, which may influence leukocytic migration. Furthermore, Menkin [*37,38*] believes that suppression of activity of the injured cell decreases the libera-

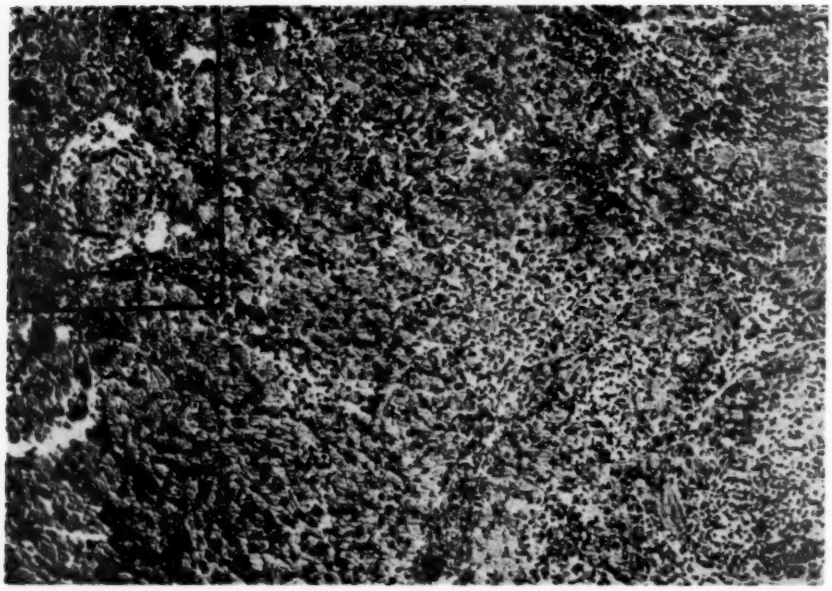

FIG. 5A. Invasive fungus proliferation in myocardium. The blood vessels are occluded by thrombi which contain numerous hyphae. The adjacent myocardium is necrotic, and there is a prominent inflammatory infiltrate; original magnification, × 150.

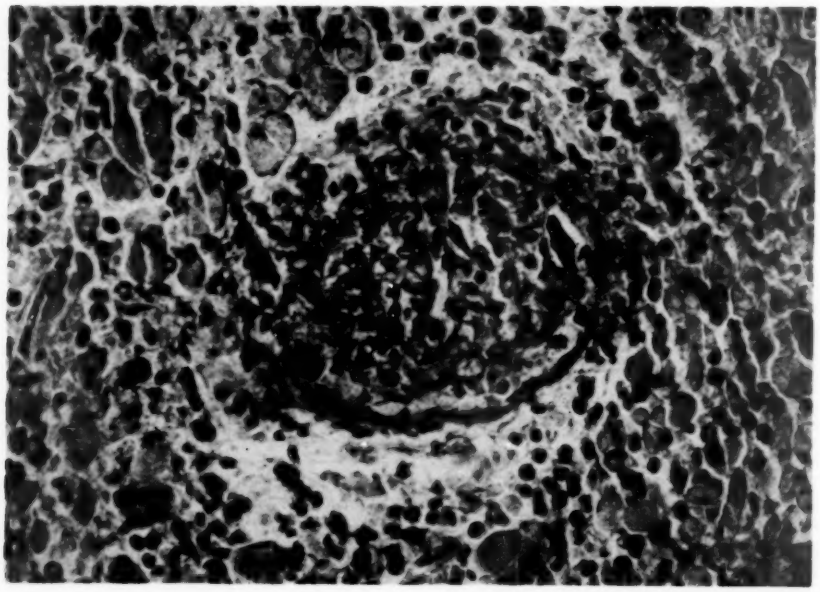

FIG. 5B. Fungi in vascular thrombus noted in Fig. 5A; periodic acid-Schiff; original magnification, × 530.

tion of leukotaxine, thereby decreasing the leukocytic response.

Many investigators have reported a depression of antibody titer following the use of steroids [*39–42*]. However, many variables apparently are involved, such as the steroid used [*40*], the species and strain of laboratory animal tested, and the type of antigen [*41*]. It appears probable that there is a depression of antibody synthesis rather than an increased antibody destruction. It further appears most probable that the depression of synthesis is due to a depression of lymphoid tissue mass. Indeed, Harris et al. [*42*] have demonstrated no suppression of activity in remaining lymphoid tissue. Thomas [*43*] advances another possibility. He believes that the depression of lymphoid tissue mass, antibody synthesis and fibroblastic pro-

liferation represent a depression of the reticuloendothelial system *per se*. Thus steroids appear to alter leukocytic response to injury due either to vascular change, direct suppression or deranged hormonal control. There is also a decreased immunologic response, probably as a result of diminished lymphoid mass. Irrespective of the mechanism, the effect of steroid activity appears to be impaired fixation and removal of microorganisms and detoxification of bacterial products.

SUMMARY

1. Thirteen cases are described in which fungus infection occurred in association with antibiotic and steroid therapy.

2. A distinction is made between surface proliferation of fungi and invasiveness into tissues. The former occurs when antibiotic therapy alone is employed; the latter is associated with combined antibiotic and steroid therapy.

3. A brief review is presented of experimental data on the role of antibiotic and steroid therapy in fungus infections.

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Aspiration Biopsy of the Parietal Pleura*

Results in Forty-five Cases

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THE presence of free fluid in the pleural cavity is not infrequently associated with considerable diagnostic difficulty from the etiologic viewpoint. When the effusion is accompanied by obvious disease processes in the lung or in other organs the etiology is more readily apparent. However, all too often the effusion is the primary feature of an illness, and after utilizing all available diagnostic methods including chemical, cytologic and bacteriologic analysis of the fluid, no obvious cause is discernible. Tinney and Olsen [*1*], were not able to uncover any etiologic factors in 38 per cent of 444 cases. Englehardt and Wilson [*2*], in 1947 studied 148 cases and classified 40 per cent as idiopathic. Recently, Leuallen and Carr [*3*] reviewed 436 cases and categorized 17 per cent as indeterminate. Obviously, the persistence and diligence with which the clinician, bacteriologist and pathologist pursue their search for an etiologic agent alter the number of "idiopathic" or indeterminate cases.

Ever since the discovery of the tubercle bacillus the association of pulmonary tuberculosis with pleural effusion has been a source of continued investigation. Roper and Waring [*4*] in their recent study of 141 cases have summarized these historic experiences. They and others [*3,5,6*] have established that the usual features of idiopathic or primary serofibrinous pleurisy with effusion, including the size, location, the characteristics of the fluid and the duration of the effusion, have definite statistical etiologic significance, but in no way can establish the cause with any degree of certainty. More important is the fact that with these same features, the inability to demonstrate tubercle bacilli, either from the aspirated pleural fluid or from culture of gastric washings or sputums, is not sufficient to eliminate tuberculosis as the cause of the effusion. This is apparent for they reported that of ninety patients whose original fluid was either inadequately studied or was negative on repeated culture, tuberculosis of one form or another later developed in fifty-nine. They further demonstrated that from close observation of this total select group, and without the benefit of chemotherapy, in 65 per cent frank evidence of pulmonary and/or extrapulmonary tuberculosis developed within a five-year period.

It is apparent that (1) from 17 to 40 per cent of pleurisy with effusion cannot be accurately diagnosed utilizing existing conventional methods; (2) an undetermined number of these represent tuberculosis and should be treated as such; (3) another undetermined percentage do not represent tuberculosis, and therefore should not be subjected to the medical, social and economic stresses attendant upon such a diagnosis, and (4) there is an urgent need for a procedure which can not only reduce the percentage of idiopathic pleurisy, and distinguish between (2) and (3), but also provide an early answer in that group which clinically fulfill all the criteria of tuberculosis pleuritis.

The use of surgical biopsy of the pleura in recent years is an attempt to provide such a procedure. The available reports in the relevant literature are few, and in some instances the biopsies were not specifically performed for diagnosis but when thoracotomy was undertaken for therapeutic reasons. Small and Landman [*7*] reported five cases of surgical biopsy, only three of which were performed specifically for diagnostic reasons. Sutliff, Hughes and Rice [*8*] performed thoracotomy in twenty-one cases in which the clinical course could not define the etiology. Stead, Eichenholz and Stauss [*9*] in an excellent

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study, discussed their findings in twenty-four patients, most of whom underwent thoracotomy for therapeutic reasons. It has also been our policy for the past two and one-half years to recommend surgical biopsy of the pleura in those cases in which we were unable to define the specific etiology by the usual methods. The results of these surgical biopsies will be the subject of a subsequent report.

There are many theoretic and practical objections to the use of surgical pleural biopsy. Quite frequently the procedure has to be performed after the acute stage of the pleurisy has subsided in order to reduce morbidity. In certain cases, specifically those of tuberculous origin, this delay does not significantly lower the incidence of obtaining a definitive diagnosis, as was adequately demonstrated in Stead's [*9*] series. Most of their procedures were performed after eight months of antituberculosis therapy, and histologic and/or bacteriologic confirmation of tuberculosis was obtained in fifteen of twenty-one. The delay does, however, significantly affect those persons who do not have tuberculous pleurisy with effusion because unnecessary observation or antimycobacterial therapy may be employed on the presumptive diagnosis of tuberculosis. Furthermore, in the patient without tuberculosis, institution of proper therapy such as radiation or radioisotopic treatment might be unnecessarily postponed. Loss of weeks of antituberculosis treatment would occur in those who do have tuberculosis. Furthermore, although the surgical procedure is not a major one, it involves some morbidity and entails considerable additional expense.

Recently, stimulated by the report of DeFrancis, Klosk and Albano [*10*], we have undertaken the use of aspiration biopsy of the parietal pleura. The experiences encountered and results obtained in forty-five cases form the basis of this report.

MATERIAL

There were forty-five patients in the series, twenty-nine men and sixteen women, of whom ten were white and thirty-five negro. The youngest was fifteen years old and the oldest, eighty-three years old.

The procedure was utilized not alone, but in conjunction with all the other standard methods of study. Initially, only those cases which were clinically thought to represent idiopathic pleurisy with effusion were included in the series. However, it soon became apparent that the procedure was valuable even in those strongly suspected of tuberculosis or malignancy. When successful it represented a safe quick method of tissue diagnosis.

There are three distinct categories of patients in whom the procedure would seem to be useful. These include: (1) serofibrinous pleurisy with effusion (clinically thought to be tuberculous); (2) effusions of malignant origin, and (3) an indeterminate group which in most instances either represented those with no obvious etiology or in which some features of the illness or clinical findings were not completely consistent with a working diagnosis of tuberculosis or malignancy.

All cases in which the diagnosis was obvious, such as traumatic hemothorax, effusion obviously secondary to cardiac failure, empyema developing after obvious pneumonia and pulmonary infarctions were excluded from the series.

At the time of biopsy all patients had either roentgenographic or fluoroscopic evidence of a pleural effusion or residual pleuritis. Some patients had more than one biopsy procedure, when either insufficient tissue was obtained initially or in order to obtain more tissue for further study. In forty-four of the forty-five cases biopsy was performed at the time of the first thoracentesis, or no diagnosis had been established as a result of earlier procedures. In the one patient (Case 16) in whom bacteriologic proof of tuberculosis had been obtained from sputum examination, a hemorrhagic effusion had developed two months after antituberculosis therapy had been instituted, and the nature of the effusion was therefore undetermined.

When the tissue obtained was inadequate, or if the result was not correlated with the clinical impression, or when non-specific inflammation of the pleura was reported by the pathologist, either a repeat aspiration biopsy was performed (if fluid was still present) or open surgical biopsy (without rib resection) was recommended.

METHOD

We have employed, with some modifications, the technic of DeFrancis and his associates [*10*]. The equipment required, in addition to the usual thoracentesis tray, is a Vim-Silverman biopsy needle and one or more straight Kelly clamps. We have omitted the skin incision as suggested by DeFrancis since it requires more time, a suture and more equipment, thereby complicating the procedure to some extent.

After the location of the fluid has been determined either by fluoroscopy or x-ray, the site for aspiration is cleansed and prepared in the usual manner. Utilizing local anesthesia, the skin and subcutaneous tissue are infiltrated down to the pleura. The pleural space is entered and fluid withdrawn, obtaining all the necessary specimens for study at this time. This is important, since not infrequently slight degrees of bleeding occur during the biopsy procedure and this would materially affect such studies as the cell count, color, specific gravity, protein, and the like.

When fluid is obtained freely the needle is withdrawn to a point at which the flow suddenly ceases. A Kelly clamp is attached to the needle at skin level. The syringe and the needle with the Kelly clamp attached is completely withdrawn, and the distance from the end of the needle to the clamp is measured and transferred to the biopsy needle. The biopsy needle with the clamp attached to it is then inserted up to the level of the clamp. This theoretically places the edge of the needle at the parietal pleura. In this manner the chances of obtaining parietal pleura are better, and of injuring visceral pleura and underlying lung less. The obturator is then withdrawn and the biopsy shaft introduced and inserted until resistance is encountered. The shaft is then advanced approximately 0.5 to 1.0 cm., followed by advancement of the outer sleeve, rotation of the biopsy shaft 360 degrees and withdrawal. Until the obturator can be replaced the orifice should be covered with the sterile gloved finger to prevent inflow of air.

TABLE I
RESULTS OF ASPIRATION BIOPSY OF THE PARIETAL PLEURA IN FORTY-FIVE CASES

Method	Number of Cases	Percentage
Diagnosed by aspiration biopsy	33	73
Inadequate tissue obtained	12	27
Total	45	100

RESULTS

Before biopsy was performed the patients were divided into three groups on the basis of clinical impressions: group I: tuberculous pleurisy with effusion, twenty-three patients; group II: malignant effusion, eleven patients; and group III: effusion of undetermined etiology (either clinically unrecognized or some features not completely consistent with either group I or group II), eleven patients. Pleural specimens were obtained in thirty-three cases (73 per cent), inadequate tissue in twelve cases (27 per cent). (Table I.) The histologic diagnoses are enumerated in Table II, and Table III contains the final diagnoses of the patients who had non-specific changes at aspiration biopsy and were subjected to surgical biopsy. In order to state that adequate tissue for diagnosis was obtained, the tissue had to satisfy the criteria outlined under the pathology section.

In group I, pleura was obtained in nineteen cases (83 per cent). Twelve patients in this group showed a granulomatous pleuritis, with or without caseation; the pleura in the other seven demonstrated non-specific pleuritis. All seven of these patients were subjected to open surgical biopsy. (Table V.) Four of these patients had evidence of granulomatous pleuritis at open biopsy and pursued clinical courses consistent with tuberculosis. In two cases open biopsy showed non-specific pleuritis, in one (Case 24) indications of both non-specific and granulomatous pleuritis were obtained (this case discussed subsequently). It would seem likely that in four cases the diagnosis of non-specific pleuritis made from specimens obtained at aspiration biopsy was incorrect since open surgical biopsy revealed a granulomatous pleuritis. One conclusion can definitely be stated: non-specific pleuritis does not rule out the presence of tuberculosis and this finding is an indication for repeat aspiration or open biopsy. (Table IV.) Of the four patients in group I in whom inadequate tissue was obtained on aspiration biopsy (Table V) two were subjected to open biopsy and

TABLE II
HISTOLOGIC RESULTS OF ASPIRATION BIOPSY IN THIRTY-THREE CASES IN WHICH ADEQUATE TISSUE WAS OBTAINED

Pathologic Diagnosis	Number of Cases	Percentage
Granulomatous pleuritis	14	42.4
Non-specific pleuritis	13	39.3
Malignancy	4	12.1
Eosinophilic pleuritis	1	3.1
Normal pleura	1	3.1
Total	33	100

TABLE III
RESULTS OBTAINED IN TWELVE CASES IN WHICH INADEQUATE SPECIMENS WERE TAKEN INITIALLY

Final Diagnosis*	Number of Cases
Granulomatous pleuritis	3
Non-specific pleuritis	5
Malignant	3
Lupus erythematosus	1

* Established by open surgical biopsy in five cases, postmortem examination in four cases, by clinical impression only in two, and bacteriologic confirmation and clinical impression in one.

gave evidence of granulomatous pleuritis. One patient refused thoracotomy but subsequently bacteriologic proof of tuberculosis was obtained. The fourth patient was found to have a pancreatic cyst which was drained surgically. The pleural effusion could have been secondary to pancreatitis. However, tubercle bacilli were obtained on gastric washing thereby raising the possibility that the effusion was tuberculous. Open biopsy however yielded pleura with non-specific inflammation.

Summarizing this group of twenty-three patients suspected clinically of having tuberculous pleuritis (Table v), twelve were proved to be tuberculous by aspiration biopsy. Seven initially found to have either non-specific pleuritis or inadequate tissue were shown to have granulomatous pleuritis at open biopsy, making a total of nineteen of tuberculous etiology. Two had non-specific involvement at both aspiration and open biopsy, one had a pancreatic cyst with non-specific pleuritis at open pleural biopsy, one refused both repeat aspiration or open biopsy. (Case 7.)

TABLE IV
RESULTS IN THE TEN CASES OF NON-SPECIFIC PLEURITIS IN WHICH OPEN BIOPSY WAS PERF· RMED *

Pathologic Diagnosis	Number of Cases
Granuloma	5
Non-specific	3
Malignancy	2
Total	10

* In three cases in this group open biopsy was not performed. However, in one of these, bronchial carcinoma was found at autopsy.

TABLE V
RESULTS IN GROUP I BY ALL METHODS

Data	Number of Cases
Diagnosed as granuloma by aspiration	12
Diagnosed as non-specific by aspiration	7
Inadequate tissue obtained	4
In all seven cases of non-specific pleuritis open biopsy was performed and results were:	
Granulomatous pleuritis	5
Non-specific pleuritis	2
Of four cases in which inadequate tissue was taken initially, open biopsy was performed in three (one refused) and results were:	
Granulomatous pleuritis	2
Not performed	1
Non-specific pleuritis	1

TABLE VI
RESULTS OF ASPIRATION BIOPSY IN GROUP II

Pathologic Diagnosis	Number of Cases
Malignancy	4
Non-specific	3 (further studies revealed carcinoma in all 3)
Normal pleura	1 (further studies revealed carcinoma)
Inadequate	3 (further studies revealed carcinoma in 2) (In one who died no autopsy was obtained)

The patients in group II were clinically categorized as having malignant pleural effusions. In these eleven patients subjected to aspiration biopsy, pleura was obtained in eight (73 per cent) and inadequate specimens were obtained in three (27 per cent). (Table VI.) Four pleural specimens yielded evidence of malignancy. Two of these specimens were highly undifferentiated carcinoma, the third was a small cell carcinoma and the fourth was interpreted as a pseudomucinous adenocarcinoma. In the other four patients in whom pleura was obtained, three demonstrated non-specific pleuritis and one a normal pleura. Two of the former patients were subjected to thoracotomy and found to have bronchogenic carcinoma with metastases to the pleura; the third, who had chylothorax, died and at postmortem examination a bronchogenic carcinoma was demonstrated. The patient showing normal pleura died and postmortem examination, limited to the chest, revealed adenocarcinoma with pleural involvement but without a primary site being determined. The remaining three patients in this group (those with inadequate specimens at aspiration biopsy) were in such poor condition that thoracotomy could not be performed. They all subsequently died. Two had evidence of metastases to the pleura at autopsy, one with

primary carcinoma of the breast and the other of the fundus of the uterus. In the final patient permission for autopsy was not granted.

In this group of patients all diagnostic procedures employed were not helpful in establishing the etiology of the effusion. These included cytologic examination of the fluid, biopsy of the scalene node, and bronchoscopy with examination of the bronchial washings for malignant cells.

Group III consisted of eleven patients who on the basis of either history, clinical manifestations (including negative tuberculin tests) or clinical course, gave no clear-cut evidence of any one disease entity (nine cases); or had heart disease of undetermined etiology with persistent pleural effusion in the face of adequate cardiac therapy, that is, seemingly refractory, (two cases). Aspiration biopsy yielded pleura in six cases (54 per cent) and inadequate tissue in five (46 per cent). Of the six from whom adequate tissue specimens were obtained, two specimens were consistent with a granulomatous pleuritis, one showed eosinophilic pleuritis, and three showed non-specific pleuritis. Of the latter three patients, only one had open thoracotomy and this revealed non-specific involvement of the pleura, pericardium and lung by biopsy. The other two had contraindications to open biopsy. They are still alive, with unchanging x-rays and clinical courses nine months and three months after biopsy and are not receiving antituberculosis treatment. (Table III.)

Of the five patients in group III with inadequate tissue obtained by aspiration biopsy, one was found to have non-specific pleuritis at open biopsy and one was subsequently found to have a pseudocyst of the pancreas which was drained surgically. Two more died and at postmortem examination were found to have non-specific inflammation of the pleura, one due to empyema from multiple lung abscesses and one without any etiologic factor being determined. However, both patients demonstrated only localized evidence of pleuritis: in one, multiple small areas, in the other, only one small area and this was at the pleuropericardial surface. The fifth patient in this group left the medical service before all studies were completed. The clinical impression was heart disease of undetermined etiology; he was recently readmitted to the hospital with congestive heart failure and no evidence of pleural effusion was apparent. Presumably the initial effusion was secondary to right heart failure. The current diagnostic impression is lupus erythematosus.

INDICATIONS AND CONTRAINDICATIONS

The prime indication for aspiration pleural biopsy is so-called idiopathic pleurisy with effusion. The method, however, may be employed when any thoracentesis is performed. We believe it should be used as part of the basic evaluation of any effusion requiring diagnostic aspiration. The only contraindication would be a bleeding diathesis. From our results we do not believe that inability to obtain fluid, in the presence of a "thickened pleura," is a direct contraindication, although the chances of obtaining tissue of diagnostic import are less. This is obvious when one considers that the presence of fluid is utilized as a guide to locate the level of the parietal pleura. Of forty-five patients, thirty-seven had free fluid. Adequate tissue, that is, tissue containing pleura, was obtained in thirty (81 per cent); inadequate specimens were obtained in only seven (19 per cent). However, in the eight patients without free fluid, pleura was obtained in only three (37 per cent) and inadequate specimens in five (63 per cent).

COMPLICATIONS

The potential dangers attendant upon this procedure are those associated with thoracentesis in general, and consist of hemorrhage, pneumothorax, spread of metastases and contamination through introduced infection. In our series, which consisted of forty-five patients with over seventy biopsies, none of these was significant. Only two patients had any complication, both small pneumothorax, which did not require intubation or even aspiration. This complication would be expected to be slight since most patients probably have early pleural symphysis. Uncontrollable hemorrhage, in a person without any blood dyscrasia, is also a rare complication. Infection is generally reported to be less than 1 per cent from thoracentesis. Since pleural effusion probably represents pleural metastases in most instances of malignancy, spread of carcinoma also seems to be of minor significance. There was no evidence of hematogenous spread of tuberculosis.

PATHOLOGY

The specimen obtained by this technic is usually a small grey white membranous fragment

measuring 1 by 3 or 4 mm. in length. We have been unable to distinguish pleura from muscle by gross appearance. However, in order to qualify as pleural tissue there must be, in addition to a membrane composed of loose or dense connective tissue contiguous to muscle, mesothelial cells lining some portion of the specimen. Tissue which contained skeletal muscle, fibrous tissue, or skeletal muscle with intervening fibrous tissue, and hemorrhagic fatty tissue (with or without signs of chronic or acute inflammation) were all considered to be inadequate specimens. It is possible however that some of these specimens were in reality examples of pleural fibrosis.

Of the fourteen patients who had evidence of granulomatous pleuritis on aspiration biopsy, all showed epithelioid granulomas, fairly typical of soft tubercles, with giant cell formation. Eight of these showed, in addition, central zones of caseation necrosis in the granulomas. Acid-fast, periodic acid-Schiff and Gridley stains were made in all granulomatous lesions, but no specific organisms could be identified. It is now our policy to submit specimens for complete bacteriologic and mycologic cultures. Histologically, granulomatous pleuritis can be demonstrated in many disease processes, the most common of which are tuberculosis, sarcoidosis, histoplasmosis, brucellosis and tularemia. However, utilizing specific skin tests and serologic studies in conjunction with the clinical course, the granuloma can usually be specifically categorized and identified. Foreign body reactions resulting from the obvious introduction of sclerosing substances such as talcum powder or suture material may produce epithelioid granulomas not unlike those found in tuberculosis but in these instances the history establishes the diagnosis.

The following cases represent typical patients in the various groups and illustrate the clinical application and usefulness of the procedure of aspiration pleural biopsy.

CASE REPORTS

CASE 2. (E-68584). A fifty-four year old unemployed white woman was admitted to the Medical Service with complaints of severe right pleuritic chest pain. Seven years previously a radical hysterectomy had been performed after histologic evidence of an adenocarcinoma of the fundus of the uterus had been established by a dilatation and curettage.

The x-ray on admission indicated the presence of a hydropneumothorax. Thoracentesis was performed on the initial hospital day and yielded 1,000 cc. of serosanguinous fluid, which subsequently did not reveal any evidence of malignancy. Simultaneously an aspiration biopsy of the parietal pleura was performed which on microscopic section was reported to contain pleura with atypical cells and unusual vesicular nuclei with scanty cytoplasm, compatible with malignancy. Subsequently, in the fifth week, a biopsy specimen of a subcutaneous nodule was again compatible with a highly undifferentiated carcinoma and two months later at postmortem the presence of metastatic carcinoma involving the right parietal pleura was demonstrated.

CASE 10. (E-69059). A sixty-five year old Negro woman was admitted to the Medical Service in a semicomatose state. No history was available initially but on physical examination, cachexia, tachycardia, a pleural effusion and marked edema of the lower extremities suggested the presence of organic heart disease with congestive failure. Subsequently a chest x-ray confirmed the presence of a pleural effusion but disclosed, in addition, infiltrations in both lungs, and densities on the pleural surface suggested the presence of malignancy. An aspiration biopsy performed during the first thoracentesis yielded hemorrhagic fluid. On histologic section the pleura appeared to be normal.

The hospital course was one of progressive deterioration. Further diagnostic studies were not undertaken since the clinical course was consistent with carcinomatosis. Some three weeks after admission the patient died and at limited postmortem examination adenocarcinoma of the lungs was demonstrable histologically.

Comment. This case demonstrates that normal pleura obtained at aspiration biopsy does not rule out the presence of disease, since metastases are apt to be studded along the pleural surface and only a relatively small area may be involved.

CASE 15. A twenty-eight year old Negro housewife was admitted to the Pulmonary Disease Division with signs and symptoms of a left-sided pleural effusion. The PPD test was positive and x-ray not only confirmed the presence of fluid but revealed evidence of consolidation of the right middle lobe. Sputum examination uncovered the presence of pneumococci, but no tubercle bacilli were demonstrable on the initial smear. The right-sided pneumonic lesion cleared rapidly after institution of penicillin therapy.

An aspiration biopsy of the pleura was performed on the day after admission, and thirty-six hours later was reported as consistent with tuberculosis with demonstration of a caseating granulomatous lesion. Appropriate treatment was instituted. An excellent response was obtained and the patient was discharged ten months later, with complete clearing of the chest. Antituberculosis treatment was continued and when

last seen thirteen months later the patient was completely asymptomatic.

Comment. Despite the accompanying pneumococcal pneumonia this patient represented a typical case of tuberculous pleurisy with effusion. Six weeks after the initial sputum and pleural fluid studies were obtained, both were reported to demonstrate the presence of tubercle bacilli. However, histologic evidence was available only thirty-six hours after admission, demonstrating the rapidity with which a diagnosis may be confirmed.

CASE 16. (E-58450). A thirty-two year old Negro truck driver was admitted to the Pulmonary Disease Division in early June, 1955. History, physical examination and x-rays were consistent with a diagnosis of far advanced active pulmonary tuberculosis. This diagnosis was corroborated by numerous specimens of sputum which contained tubercle bacilli on smear and culture. Treatment with an experimental regimen consisting of PAS and cycloserine, 12 gm. and 1.0 gm. respectively, was instituted. Five weeks later no significant response had been obtained and physical examination suggested the presence of a pleural effusion which was confirmed by x-ray and at thoracentesis when 850 cc. of serosanguinous fluid was obtained. Reaccumulation of the fluid was rapid and required removal frequently. The inability to demonstrate acid-fast bacilli in the pleural fluid and the rapid reaccumulation of the sanguinous fluid, despite seemingly adequate dosages of antituberculosis therapy suggested the possibility of other etiologies as the cause of the effusion. On August 17, 1956, an aspiration biopsy of the parietal pleura was consistent with a caseating granulomatous pleuritis.

Salizid® was substituted for cycloserine and soon thereafter clinical improvement was noted, with absorption of the fluid, conversion of the sputum, defervescence, return of appetite and significant weight gain. The patient was discharged ten months later for continued treatment.

CASE 18. A fifty-three year old Negro man was admitted to the Medical Service in September, 1955 for the fifth time with recurrent left pleural effusion. In the one year prior to this admission he had been hospitalized on four separate occasions for congestive heart failure. There was radiographic evidence of a left pleural effusion on each admission and thoracentesis was performed but at no time was the presence of tubercle bacilli demonstrated. No definite etiology of the heart disease was determined. On each occasion a strict cardiac regimen resulted in relief of heart failure and the pleural space was clear radiographically at the time of discharge.

On the fifth admission an aspiration biopsy of the pleura yielded evidence of a caseating granuloma. The diagnosis of chronic constrictive pericarditis was made and was corroborated by cardiac catheterization. Subsequently a pericardiectomy was performed and examination of the tissue again yielded a caseating granuloma. Postoperatively, all signs of congestive failure disappeared and the patient is now completely asymptomatic.

Comment. The fluid obtained at thoracentesis never yielded any evidence of tubercle bacilli on any occasion prior to the pleural biopsy. Although constrictive pericarditis had been considered, the inability to establish the etiology of the pleural effusion by all available criteria suggested that the effusion was secondary to the failure. The biopsy confirmed the presence of granulomatous disease and helped establish the diagnosis.

CASE 19. (E-66586). A fifteen year old Negro girl was admitted to the Medical Service with a five-week history of cough, fever, chills and left pleuritic chest pain. One week after the initial onset a private physician had examined the patient, made a diagnosis of pneumonia and recommended a ten-day course of treatment with tetracycline. A subjective response to this regimen was obtained but with reappearance of the symptomatology hospitalization was recommended.

On admission the presence of a small left pleural effusion was detected by x-ray. Thoracentesis was performed in conjunction with aspiration biopsy. The fluid was sterile on culture and histopathologic section yielded non-specific chronic inflammatory changes in the pleura. Clinical, radiographic, fluoroscopic and electrocardiographic results were also compatible with a pericardial effusion. The pleural fluid rapidly disappeared and a second aspiration biopsy was unrewarding. Three weeks later open surgical biopsy yielded pleural tissue with evidence of a caseating granulomatous pleuritis. Appropriate antituberculosis treatment was started. The subsequent course was compatible with tuberculous pleurisy with effusion. Cardiac catheterization was performed in February, 1956. Normal pressures were noted in the right heart and pulmonary circuit. The patient was discharged eleven months after admission.

CASE 24. (E-68784). A fifty-three year old white man was admitted to the Pulmonary Disease Division for diagnosis and treatment in October, 1955. Two years previously a routine x-ray had demonstrated a parenchymal lesion in the left upper lobe. After an unknown period of observation with no demonstrable change on serial films he was told that this probably represented inactive tuberculosis, although bacteriologic studies were not performed. Two months prior to admission a repeat x-ray was taken,

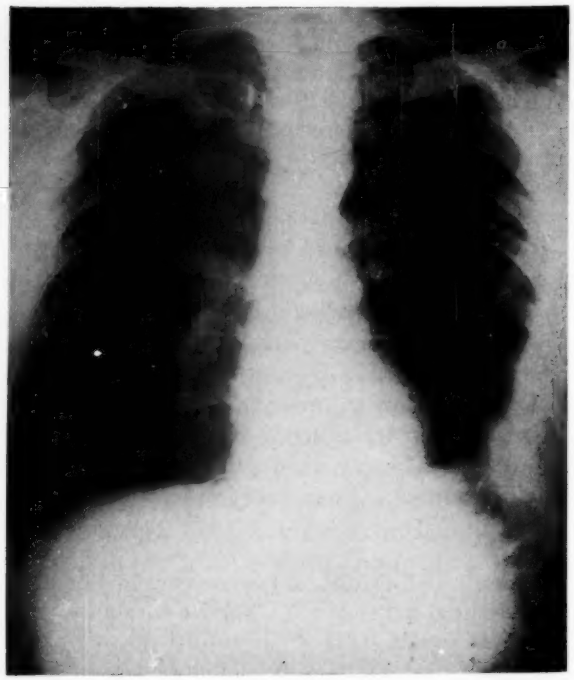

FIG. 1A. Case 24. Roentgenogram showing left pleural effusion and left apical infiltration.

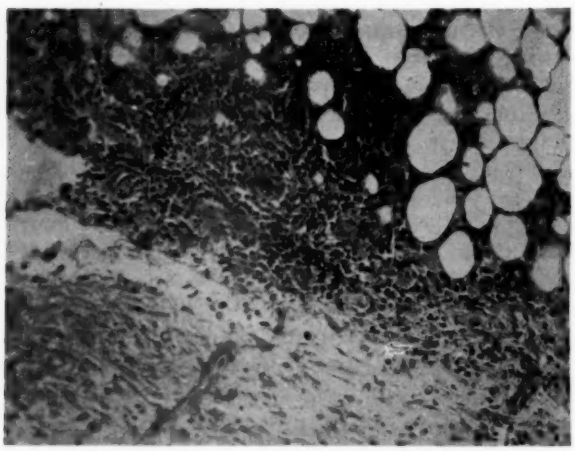

FIG. 1B. Case 24. Microscopic section of pleura in area of the effusion obtained by aspiration biopsy, demonstrating non-specific inflammation.

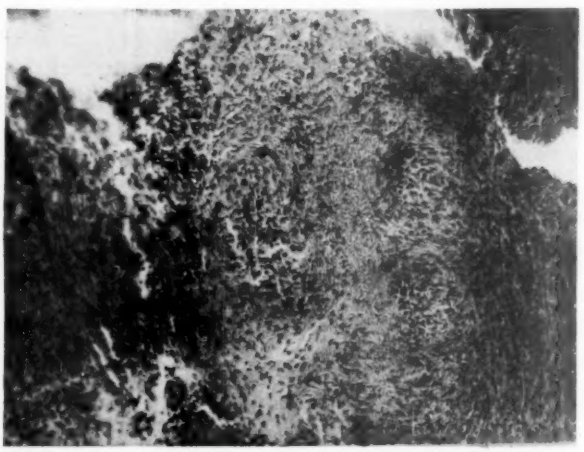

FIG. 1C. Case 24. Section of the parietal pleura in the region of the pulmonary infiltration obtained by surgical biopsy, demonstrating a granulomatous pleuritis.

after the onset of anorexia, fever and weight loss. An x-ray on admission demonstrated a parenchymal infiltrate in the left upper lobe and a small pleural effusion. Repeated attempts at thoracentesis were not rewarding. On the basis of the history and roentgenographic findings, indicating tuberculosis, therapy consisting of biweekly streptomycin and daily PAS was instituted shortly after admission. The course was uneventful until January, 1956 (two months after treatment was started) when left pleuritic chest pain occurred and the fluid in the left chest increased. (Fig. 1A.) An aspiration biopsy of the parietal pleura yielded tissue consistent with a non-specific inflammation of the pleura. (Fig. 1B.)

Two weeks subsequently an open biopsy was recommended because of the inconclusive results of the aspiration biopsy and since bone marrow and gastric cultures obtained on admission were reported to be negative. Biopsy of the pleura was obtained at two levels, inferiorly at approximately the same level at which the aspiration biopsy was performed, and superiorly at a level contiguous to the parenchymal infiltration. On microscopic section the pleura at the lower level also showed non-specific pleuritis, but the biopsy taken superiorly disclosed pleural changes consistent with a non-caseating granuloma. (Fig. 1C.) Postoperatively the course was normal and at present the patient is completely asymptomatic.

CASE 39. A fifty-six year old Negro man was referred to the Medical Service from the Diagnostic Clinic with a presumptive diagnosis of tuberculosis. The only complaints were a non-productive cough and right pleuritic chest pain both of three weeks' duration. The significant findings on physical examination were those of fluid or thickened pleura in right chest, with limitation of motion of the right hemidiaphragm. The liver was enlarged, hard, irregular, nodular and non-tender. X-ray is shown in Figure 2A.

Shortly after admission the right pleural effusion increased and 1,500 cc. of serosanguineous fluid was removed which was negative for malignant cells. However, a pleural biopsy performed simultaneously yielded pleura with numerous areas of malignant cells forming acini which were also present in underlying stroma and lymphatics, consistent with metastatic adenocarcinoma. (Fig. 2B.) A subsequent pleural

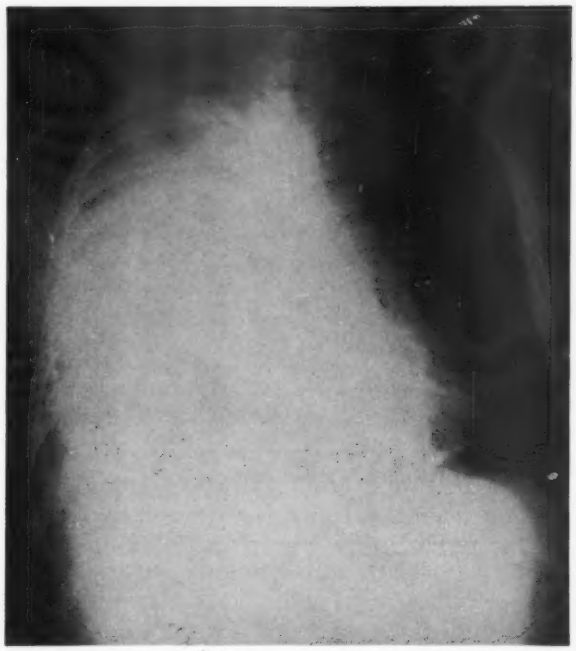

FIG. 2A. Case 39. Chest x-ray showing a massive right pleural effusion.

fluid specimen was interpreted as class v with definite malignant cells present.

A thorough search for the primary lesion, including liver biopsy, was unrewarding. The patient's condition gradually deteriorated, he exhibited evidence of central nervous system involvement, probably metastatic, and died sixty days after admission. Permission for postmortem examination was not granted.

Comment. Aspiration pleural biopsy furnished the first "proof" of malignancy although the clinical findings were not only completely compatible but strongly suggested this diagnosis.

CASE 45. A seventy year old Negro man was admitted to the Pulmonary Disease Division with a three-week history of right pleuritic chest pain and a 20 pound weight loss. Physical examination revealed no abnormalities except for signs of fluid in the right chest (Fig. 3A) and evidence of significant anemia. Sigmoidoscopy was performed and a polypoid lesion was seen. Despite the absence of any gastrointestinal symptomatology, barium study of the upper intestinal tract was ordered and demonstrated a filling defect in the antrum of the stomach which was thought to represent a malignant lesion.

An aspiration biopsy of the pleura was reported as demonstrating a caseating granuloma. (Fig. 3B.) Two weeks later, after appropriate antituberculous treatment had been started, and a repeat upper gastrointestinal series had reconfirmed the lesion, laparotomy was performed. The findings were consistent with a malignant lesion of the stomach. However, in addition to a biopsy of the mass which demonstrated carcinoma, biopsy specimen of a regional node in the mesentery was consistent with a caseating granuloma. (Fig. 3C.)

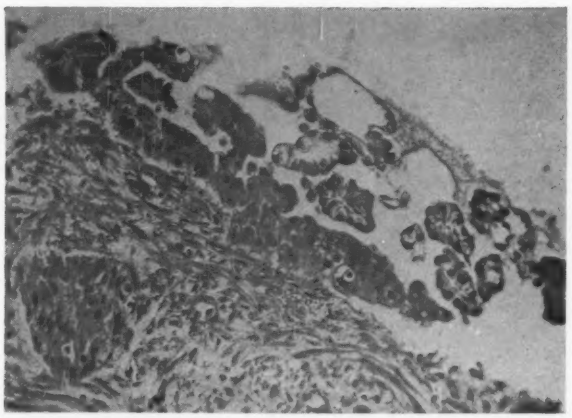

FIG. 2B. Case 39. Microscopic section obtained by aspiration biopsy, demonstrating adenocarcinoma.

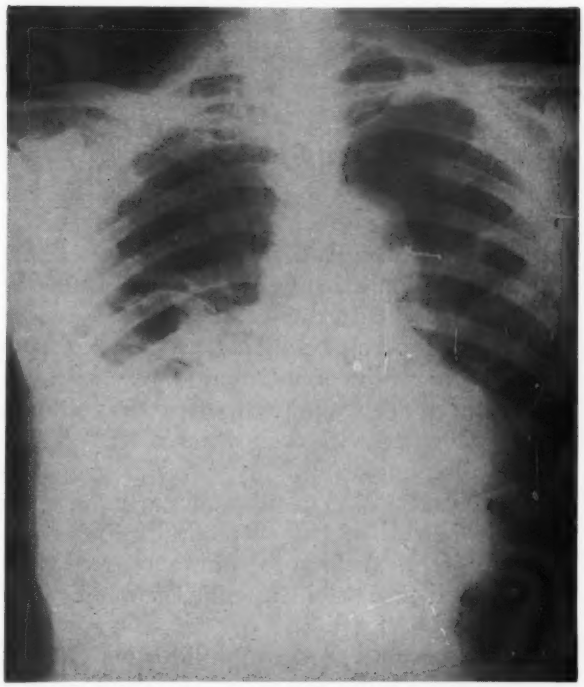

FIG. 3A. Case 45. X-ray of chest showing right pleural effusion.

Some weeks later, after an unexplained hypotensive episode, the patient suddenly died. A limited postmortem examination confirmed the presence of both tuberculosis of the nodes from the mesentery and carcinoma of the stomach. In addition there were findings indicative of a pleuritis of tuberculous origin.

COMMENTS

There is great need for a simple, safe and effective technic for definitely establishing the

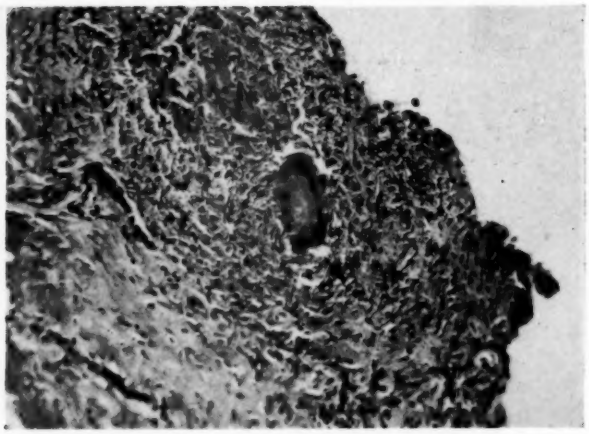

FIG. 3B. Case 45. Aspiration biopsy showing granulomatous pleuritis.

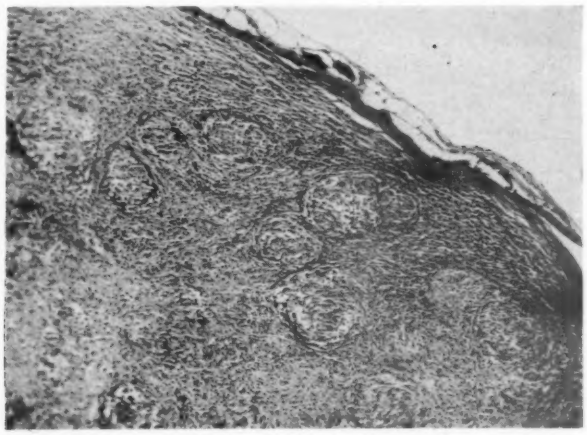

FIG. 3C. Case 45. Microscopic section of the lymph node adjacent to stomach, demonstrating granuloma.

etiology of pleural effusion. Current diagnostic methods often fail and one must then rely on assumptions and observation for guidance. Unfortunately, assumptions may prove erroneous and protracted observation may increase morbidity and even mortality. The incidence of success in isolating tubercle bacilli from tuberculous pleural effusion varies from laboratory to laboratory and with the technic of examination. In general, tubercle bacilli can be cultured from about 25 per cent of tuberculous pleural effusions. This usually requires many weeks and such a delay, coupled with the low incidence of positive results, makes this type of examination rather impractical. Yet tuberculosis is the main problem in this matter of pleural effusion because this diagnosis, so often presumptive, carries such serious therapeutic, economic and prognostic implications.

Cytologic study of pleural fluid is helpful and produces positive results in about 50 per cent of cases of malignant effusions when the examination is performed expertly. However, when the clear fluid does not reveal malignant cells a mistaken diagnosis of tuberculosis not infrequently is made. In addition, false positive diagnoses occur because of the confusion resulting from the similarity between malignant and mesothelial cells, especially when the latter are in the process of dividing and possess mitotic figures.

Furthermore, although certain characteristics of pleural fluid are usually present in specific conditions, there is an overlap which makes full reliance on the features of the fluid dangerous. This holds true for determinations of specific gravity, total and differential white cell count, erythrocyte count, protein and sugar. Admittedly, certain clues may be forthcoming from these studies but they do not permit a precise diagnosis.

Aspiration biopsy of the parietal pleura has provided a simple and accurate method for determining the etiology of most pleural effusions. It is as easy to perform as a thoracentesis and as free of complications. One of the most desirable aspects of this form of biopsy is that it can be executed at the time of thoracentesis and usually provides a pathologic diagnosis within twenty-four to forty-eight hours. Thus in fourteen of our patients with tuberculous pleural effusion, aspiration pleural biopsy was the first proof of the cause and was available in most instances before the first twenty-four-hour sputum specimen had been received in the laboratory. Similarly, in the carcinoma group it was often the quickest method of diagnosis and in more than 50 per cent of the cases, provided the only tissue diagnosis.

The accuracy of aspiration pleural biopsy is attested by confirmation of the diagnosis by other means, including clinical course, bacteriologic proof and histopathologic findings in other tissues including those obtained at necropsy. In our series the diagnosis of tuberculous pleuritis or malignancy made on pleural biopsy was corroborated in every case.

It must be emphasized that non-specific inflammatory changes of the pleura should not be accepted as a specific diagnosis, since this may lead to errors. This is readily apparent when one realizes that the aspirated tissue containing parietal pleura may not be representative of the entire pleura. This situation obtains

frequently in metastatic malignant involvement of the pleura in which islands of malignant tissue occur. Obviously, the aspirated parietal pleura may not be among areas of malignant invasion. In tuberculous pleural effusion the pleura is usually diffusely studded with tubercles and therefore positive tissue is obtained at any site of aspiration. Occasionally, however, the pleura reveals granulomatous formation only in the region of the subjacent pulmonary tuberculous lesion while the remainder of the pleura shows a non-specific pleuritis.

The finding of non-specific pleuritis often indicates the need for open surgical pleural biopsy for precise diagnosis. Open surgical pleural biopsy was performed in ten of our thirteen patients in whom non-specific inflammatory changes were noted on aspiration biopsy. In five, granulomatous pleuritis was noted; in two, carcinomatous tissue was obtained. The remaining three patients showed non-specific pleuritis even after a complete exploratory thoracotomy. The precise implications of this finding remain to be elucidated. Careful follow-up examination may clarify this problem. It is entirely possible, although admittedly conjectural, that these cases are examples of an entity, benign non-specific pleuritis, not unlike its pericardial counterpart, benign non-specific pericarditis. That some are expressions of lupus erythematosus cannot be denied.

The incidence of failure to obtain an adequate specimen is directly proportional to the experience of the person performing the biopsy. Most of our failures occurred early in the study. We have found it desirable to obtain several bits of tissue through the same initial needle puncture while varying the direction of the biopsy needle. This not only increases the likelihood of obtaining pleura but has the added advantage of decreasing the incidence of false negative reports when the pleura is not diffusely involved. Currently, we resort to open pleural biopsy only when at least three aspirated pleural specimens have been examined and do not yield a specific tissue diagnosis.

SUMMARY

1. There is definite need for additional diagnostic procedures to help establish the etiology of pleurisy with effusion.

2. Aspiration biopsy of the parietal pleura is a safe, easy and accurate method of accomplishing this and may be extremely valuable in obtaining an early diagnosis.

3. In forty-five cases in which this procedure was utilized, diagnostic tissue was obtained in 73 per cent.

4. The histologic diagnosis of non-specific pleuritis does not eliminate the possibility of either tuberculosis or malignancy as the etiologic cause. In persons in whom this diagnosis is made after aspiration biopsy, an open biopsy should be performed if not contraindicated.

5. Aspiration biopsy was of considerable value in a group of patients suspected of tuberculosis, giving a definite tissue diagnosis in 83 per cent.

6. In eleven patients with pleurisy with effusion classified clinically as "indeterminate," aspiration biopsy of the parietal pleura yielded diagnostic tissue in 54 per cent.

7. The procedure is less useful in patients with malignancy with pleural involvement.

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The Significance of Bronchiectasis Associated with Pulmonary Tuberculosis*

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CHEST physicians, thoracic surgeons, roentgenologists and pathologists have been cognizant of the occurrence of bronchial disease in pulmonary tuberculosis for many years. No general agreement has been reached regarding the pathogenesis or clinical significance of bronchiectasis associated with tuberculosis. Amberson [*1*], Medlar [*2*] and others appear to doubt that tuberculosis is responsible for bronchiectasis. They maintain that its presence in areas of tuberculous involvement is fortuitous. Hinshaw [*3*] mentions that bronchiectasis occasionally occurs with tuberculosis. Olson [*4*] examined 602 lung specimens resected from tuberculous patients and concluded that tuberculous bronchiectasis occurred in 42 per cent of the patients. Recently Corpe and Hwa [*5*] reported 40 per cent of their surgical specimens revealed tuberculous bronchiectasis. Juhl [*6*] has just completed a careful x-ray investigation of one hundred tuberculous patients in whom bronchograms and planigrams had been obtained. He compared the usefulness of these procedures in diagnosing bronchiectasis. The study showed that more than half of this group of patients with tuberculosis had roentgenologic evidence of bronchiectasis.

Controversy in regard to the entity of tuberculous bronchiectasis has tended to minimize the true importance of this condition. During the last ten years, review of over 1,000 cases presented at "lung cutting" has allowed the correlation of clinical course, x-rays, bacteriology and pathology of resected specimens. It is the purpose of this paper to draw attention to the important pathologic and clinical aspects of the concept of tuberculous bronchiectasis.

Etiology of Bronchiectasis. The mechanism of non-tuberculous bronchiectasis formation is obscure. The cystic variety may be attributed to congenital defects or malformation of the bronchi in the development of the lung [*7*]. The saccular and cylindrical forms may be congenital [*8–10*] and associated with such anomalies as fibrocystic disease of the pancreas [*11*] and Kartagener's triad [*12*]. An acquired form may occur following whooping cough [*13*], sinusitis [*14*], recurring bronchitis, pneumonia [*15–17*] and bronchial obstruction [*18*]. Follow-up studies of tuberculous patients over many years make it possible to ascertain the manner in which bronchiectasis develops in this disease. There are three principal factors which appear to favor the dilation, distortion, disorganization of bronchial walls and tuberculous involvement of bronchi. These will be illustrated by typical case reports.

A rare form is established usually in childhood as a result of enlarged tuberculous hilar nodes compressing a bronchus, inflammatory reactions surrounding these areas or perforation of the bronchus [*19–21*]. Partial obstruction with cough, pooling of secretions and tubercle formation in the more distal portion of the bronchial tree comprise the elements which lead to bronchiectasis.

CASE 1. S. O., an eight year old boy had a cough and recurring bouts of fever for one year. Gastric cultures were positive for acid fast bacilli. An x-ray (Fig. 1) showed enlarged hilar nodes compressing the bronchus of the middle lobe, causing atelectasis. The patient received streptomycin and para-aminosalicylic acid for six months with considerable clearing on x-ray. Bronchograms nevertheless revealed bronchiectasis. When the lobe was resected the surgeon encountered difficulty in dissecting out the ring of firm, constricting glands. Gross and microscopic pathologic sections demonstrated bronchiectasis.

The second and most common cause of tuberculous bronchiectasis is severe infiltration of the lung with tuberculous disease, frequently asso-

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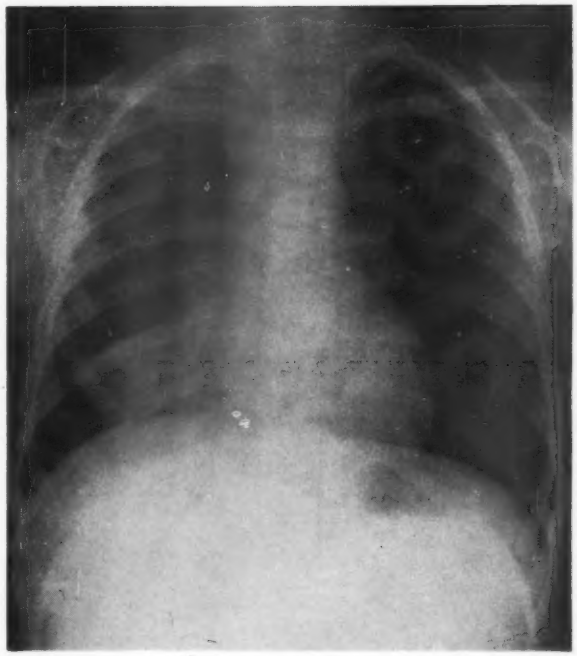

FIG. 1. O. S., an eight year old boy. X-ray shows enlarged hilar nodes and atelectasis of right middle lobe.

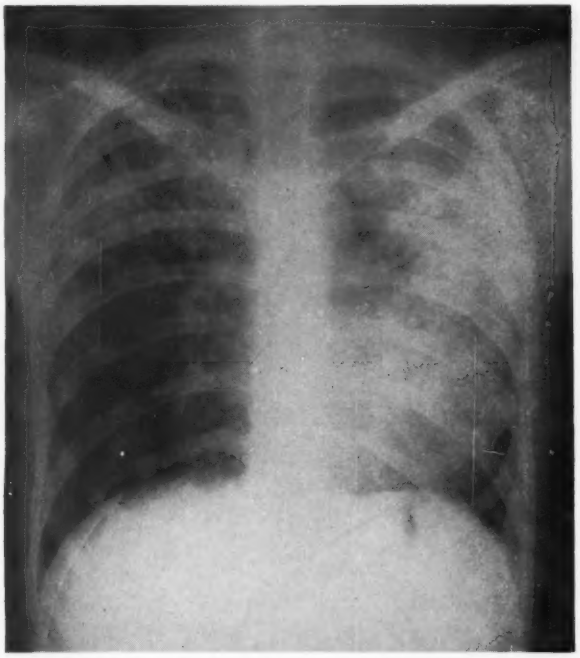

FIG. 2. G. B., a twenty-seven year old man. X-ray of the chest shows extensive infiltration in left lung, infiltration in upper half of right lung and large cavity.

ciated with a cavitary component [*22*]. Although almost complete clearing of the parenchyma may take place, residual bronchiectasis often remains, just as emphysema is a frequent silent partner of tuberculosis [*23*]. Bronchiectasis, however, is readily demonstrable by planography or bronchography.

CASE II. G. B., a twenty-seven year old white man had widespread pulmonary infiltration in October, 1947. (Fig. 2.) With bedrest and several courses of streptomycin and pneumoperitoneum treatment he showed considerable improvement on x-ray. He was eventually discharged from the sanatorium after two years and eight months of treatment, but pneumoperitoneum was continued. Nevertheless, he returned to the hospital sixteen months later because of a brisk hemoptysis following a severe upper respiratory infection. Gastric cultures were again positive. Bronchograms (Fig. 3) of the right side revealed cylindric bronchiectasis with terminal stenosis near the area of former cavity. Bronchograms of the left side (Fig. 4) demonstrated saccular bronchiectasis throughout the left upper lobe. Note that this extended to the periphery of the lung. Bilateral bronchiectasis was the indication for resection after four months of treatment with streptomycin and para-aminosalicylic acid. Pathologic sections confirmed the presence of bronchiectasis.

Another common condition is tuberculous endobronchitis which may lead to destructive changes in the bronchial walls resulting in bronchiectasis [*24*].

CASE III. A persistent cough following an upper respiratory infection in April, 1948 developed in L. D., a twenty-nine year old male student. A sputum smear revealed many tubercle bacilli. Although little parenchymal disease was apparent in the x-ray, bronchoscopy showed extensive tuberculous bronchitis of the left lower lobe. He was treated with two brief courses of streptomycin, 1 gm. daily for one month each. He spent fourteen months in a sanatorium. Thereafter, he was observed periodically in the student health clinic. In February, 1953 an infiltration appeared in the left lower lobe. Bronchograms showed bronchiectasis which was confirmed by resection of the left lower lobe after six months of streptomycin and para-aminosalicylic acid therapy. Figure 5 shows extensive bronchiectasis and some small caseous foci. The microscopic section (Fig. 6) reveals two large caseous tubercles immediately under the epithelial lining of a dilated bronchus. Considerable activity is present in spite of six months chemotherapy.

Clinical Features of Tuberculous Bronchiectasis. The above patients illustrate the close association of tuberculous lesions with the subsequent finding of bronchiectasis in the same areas. The high incidence of bronchiectasis in the upper lobes, associated with tuberculosis, is noteworthy. Situated in this site, bronchiectasis may

FIG. 3. G. B., a twenty-seven year old man. Right bronchogram showing bronchiectasis below area formerly occupied by cavity.

FIG. 4. G. B., a twenty-seven year old man. Left bronchogram showing saccular bronchiectasis involving left upper lobe extending out to the periphery in the lingula.

display lesser symptomatology. The clinical features when present are persistent cough and purulent sputum, often tending to subside under antimicrobial therapy. Hemoptysis may be a troublesome occurrence. Protracted bronchitis following an upper respiratory infection is a common sequence. At this time the sputum is most apt to be positive for tubercle bacilli.

CASE IV. D. W., a thirty-five year old white man had tuberculosis in 1944. His treatment consisted of left phreniclasia and sanatorium care for fourteen months. Ten years later, following upper respiratory infection, he had hemoptysis and positive sputum in August 1955. Posteroanterior stereoscopic films were normal except for a somewhat elevated left diaphragm. Lateral planigrams revealed bronchiectasis, confirmed by resection of the left lower lobe.

Significant Pathologic Features of Tuberculous Bronchiectasis. Certain pathologic features found in resected lungs involved with tuberculous bronchiectasis are worthy of emphasis. First, tubercles often lie very close to the epithelial surface. This is a dangerous situation, especially when the overlying membrane is ulcerated and ragged. Olson [*4*] found endobronchial tuberculosis in over half his cases of bronchiectasis. Only slight ulceration such as occurs with non-specific bronchitis may liberate caseous material containing tubercle bacilli into the bronchial tree. Secondly, many bronchiectatic lesions have been shown to communicate with cavities or liquefying nodular disease, hence providing a ready source for long-continued positive secretions. Thirdly, the bronchial walls may be greatly thickened by fibrous tissue and the scarring in the surrounding lung tends to distort and pull the diseased bronchi together. This walling off by dense fibrous tissue hinders the penetration of antimicrobial drugs. Hence, nests of tubercle

FIG. 5. L. D., a twenty-nine year old man. Pathologic section through left lower lobe revealing extensive saccular bronchiectasis, best seen in lower portion of photograph.

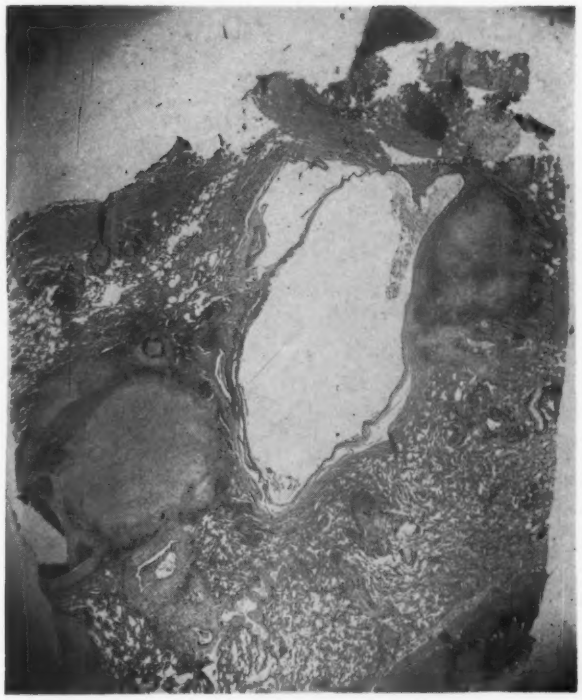

FIG. 6. L. D., a twenty-nine year old man. Photomicrograph of a dilated bronchus showing two large tubercles beneath the epithelial surface.

bacilli lodged in these sheltered areas lie dormant and may not be exposed to adequate concentrations of chemotherapeutic agents. When liberated these organisms may cause further disease. That bacilli in such diseased tissue can survive long periods, even under intensive antimicrobial therapy, is illustrated by the following patient.

CASE V. M. T., a twenty-eight year old Negro student was first discovered to have tuberculosis while in the Navy in 1945. Later he was treated in hospitals continuously for over nine years with the exception of three months in 1954. Streptomycin, para-aminosalicylic acid or isoniazid were given for over five years, primarily for bone tuberculosis complicated by moderately advanced pulmonary disease. Following transfer to our hospital bronchograms showed evidence of extensive bronchiectasis in the right upper lobe and to a lesser degree in the middle lobe. Although secretions had been negative for acid-fast bacilli for twenty months, resection of these lobes was carried out. Figure 7 illustrates the type of bronchiectasis present. The dense fibrous tissue on gross examination was difficult to differentiate from carcinoma. Smears and cultures from the specimen were positive for acid-fast bacilli. It is significant that these organisms were still sensitive to all three drugs, indicating that they had not been exposed to adequate concentrations of the drugs to eradicate them nor sufficient amounts to convert them to resistant organisms.

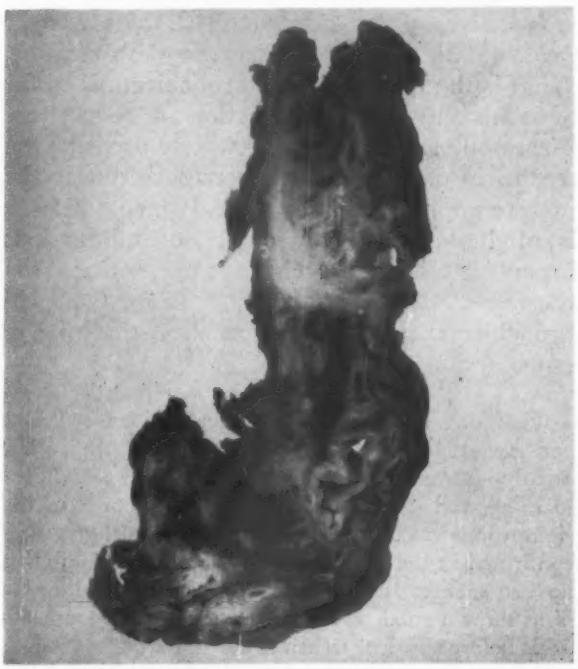

FIG. 7. M. T., a twenty-eight year old man. Pathologic section through right upper lobe demonstrating extensive bronchiectasis and dense fibrosis.

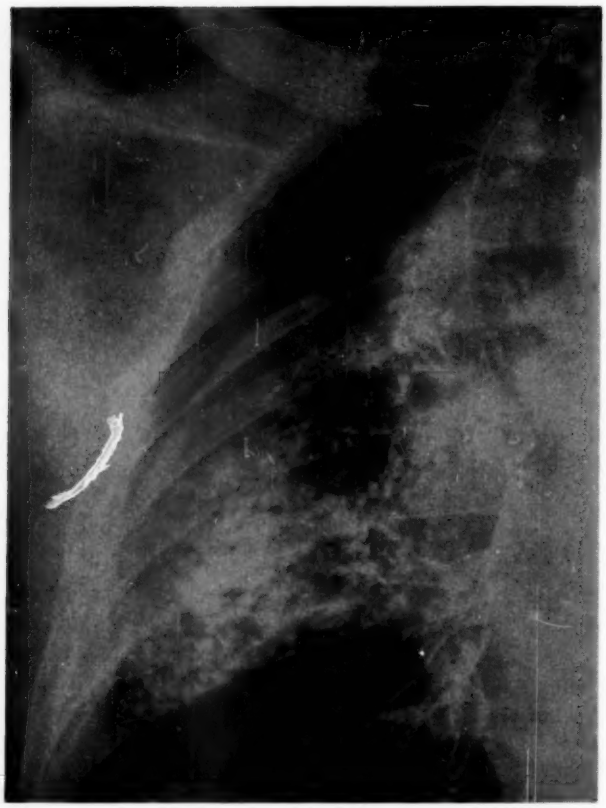

FIG. 8. T. Y., a thirty-one year old man. Bronchogram of right lung showing bronchiectasis in right upper lobe beneath the pneumothorax.

Importance of Bronchiectasis in Collapse Therapy and Surgical Resection of Pulmonary Tuberculosis. What is the importance of bronchiectasis so far as collapse therapy and resection are concerned? Pneumothorax is no longer widely used for the treatment of pulmonary tuberculosis due to the many complications that occur. If pneumothorax is attempted in the presence of tuberculous bronchiectasis, focal atelectasis may ensue. Furthermore, the fibrosis which takes place in bronchiectatic areas may not allow the lung to re-expand eventually.

CASE VI. T. Y., a thirty-one year old colored man had a right pneumothorax for eight years and a left pneumothorax for seven years. The right side failed to re-expand due to extensive bronchiectasis in the right upper lobe, shown on bronchogram (Fig. 8) and confirmed in the resected specimen. The left side had no bronchiectasis and re-expanded well. Follow-up films show a good result in a patient with poor prognosis before surgical treatment.

Primary thoracoplasty also has been abandoned in most hospitals. The frequent relapses after this type of surgery are attributed to nonclosure of cavities and the presence of bronchiectasis. The collapse therapy may cause further distortion, inhibit drainage and allow smoldering disease to continue.

CASE VII. D. B., a twenty-six year old white man had one year of chemotherapy and thoracoplasty in 1952. He had a relapse in May, 1955. Bronchograms (Fig. 9) demonstrated extensive bronchiectasis under the thoracoplasty, confirmed by resection of the left upper lobe.

The present vogue in the surgical treatment of pulmonary tuberculosis is resection [*25*] of cavitary and residual disease during an adequate period of chemotherapy. Relapses or surgical failures are infrequent. They are most often due to reactivation of old disease, remaining potential cavitary disease, new disease, bronchiectasis, bronchopleural fistula and tuberculous granulating bronchial stump often with exposed suture material seen on bronchoscopy.

In recent years removal of a portion of a lobe has been widely practiced [*26*]. The technic of segmental resection allows the surgeon to save good tissue within a lobe. It is important that he know the status of the bronchi within the lobe to be subjected to segmental dissection. The pathologist appreciates that the bronchiectatic involved bronchi often are distorted and may approach the pleural surface of the lung and indeed may be the cause of spontaneous bronchopleural fistula and empyema. Likewise, the dilated bronchi may be located near the segmental plane, as shown schematically in Fig. 10. On the left is the more common partial stenotic type of bronchiectasis which is not apt to lead to tuberculous complications following surgery. The saccular bulbous type, as depicted on the right, would seem to be particularly hazardous if a caseous focus extends across the segmental plane. The unsuspecting surgeon will include this focus in his specimen, little realizing that he may be dissecting into small dilated bronchi which have thick, irregular infected walls. They tend to remain open unless carefully sutured, and still may break open just as infected bronchial stumps tend to do following lobectomy or pneumonectomy [*27*]. A review of our eight patients in whom bronchopleural fistula developed following segmental resection, requiring a secondary procedure, showed that in four a dilated bronchial opening was found and sutured. One was described by the surgeon as coursing along the raw segmental plane surface.

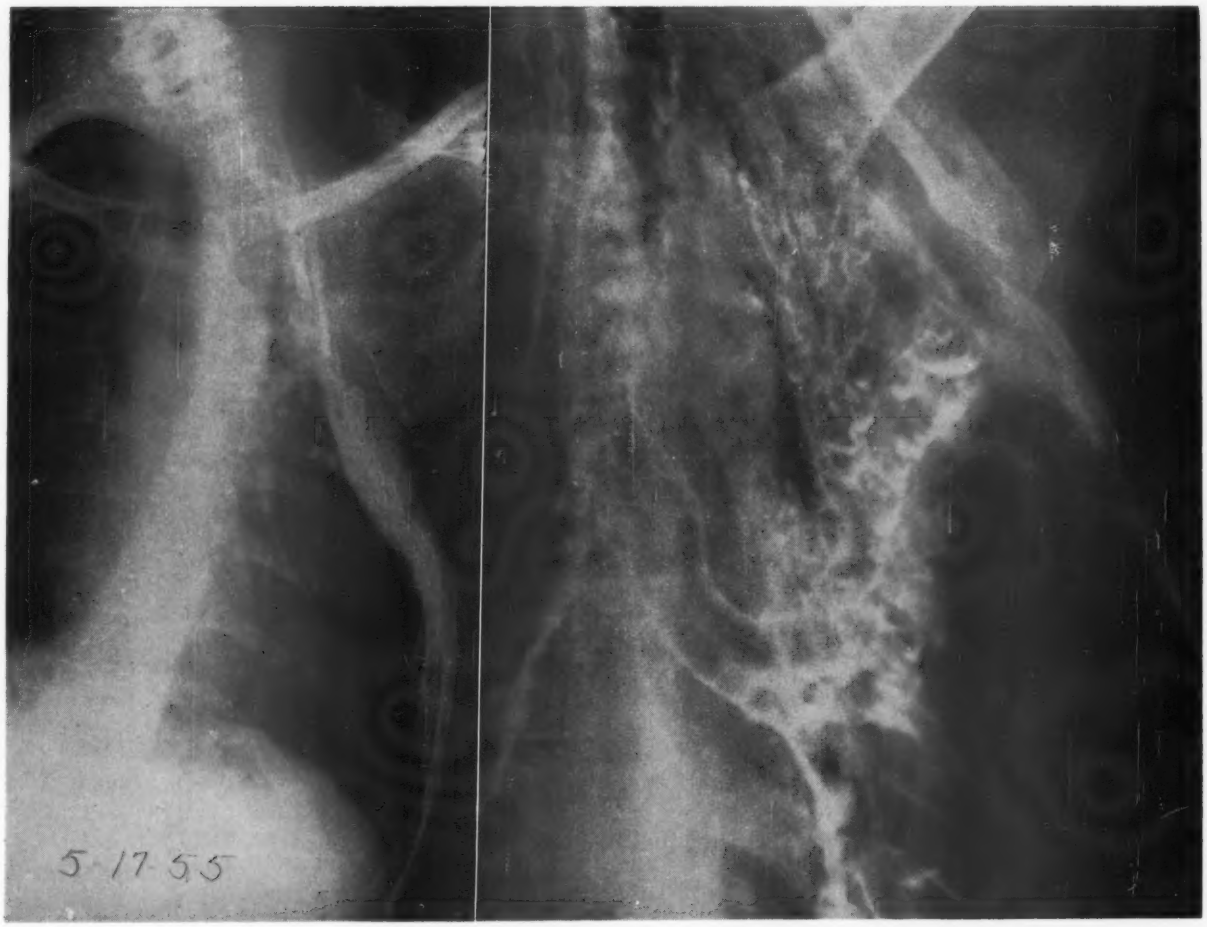

FIG. 9. D. B., a twenty-six year old man. X-ray shows left thoracoplasty. Bronchogram on the right shows extensive bronchiectasis involving left upper lobe which is compressed by thoracoplasty.

A group of thirteen patients, comprised of those whose sputums remained positive or who had a relapse bacteriologically following segmental resection, were reviewed. (Table I.) The indication for the original surgery in most cases was cavitary disease. Five patients came from other hospitals following segmental resection and eight from our own group. All except one had preoperative chemotherapy for six months or

TABLE I
DATA ON 13 PATIENTS* WITH BACTERIOLOGIC RELAPSES OR POSITIVE SECRETIONS AFTER SEGMENTAL RESECTION

Diagnosis		
Moderately advanced	6	
Far advanced	7	
Average age of patient	34.5	years
Average duration of disease	18	months
Average duration of chemotherapy before surgery	13	months
Continuous combined therapy before surgery	11	patients
Relapse after discharge	6	patients
Positive secretions in hospital after surgery	7	patients
Resistant organisms in sputum or resected specimen (12 tested)	6	patients

* Eight patients from our group of over 500 segmental resections, 5 patients from other hospitals. Detailed follow-up is not yet available on the entire group of 500.

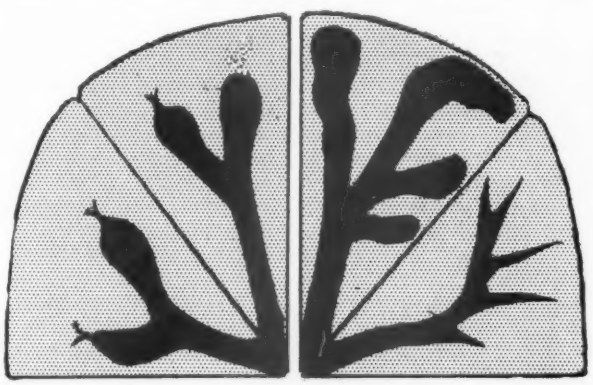

FIG. 10. Schematic diagram of bronchiectasis associated with tuberculosis.

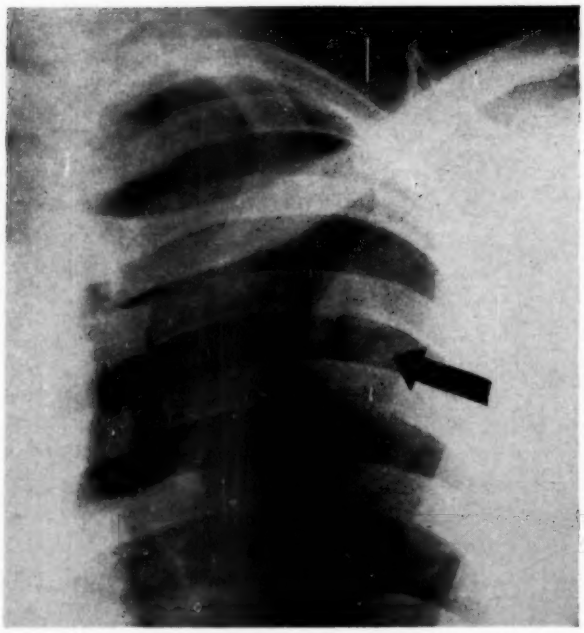

FIG. 11. M. A., a twenty-three year old man. X-ray of the chest demonstrating small thick-walled cavity in left upper lobe.

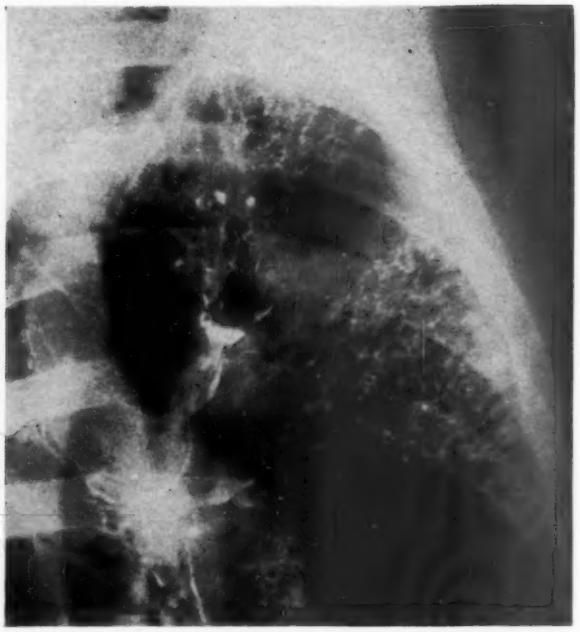

FIG. 12. M. A., a twenty-three year old man. Bronchogram reveals cavity with dilated bronchial communication in left upper lobe in the area of previous segmental resection.

more. Eleven of these patients received continuous antimicrobial therapy until the time of surgery. Postoperative chemotherapy was adequate in all except one patient who received drugs to which his organisms were not sensitive. About half the patients demonstrated resistant organisms to one or more drugs in the sputum or resected lungs. Six relapsed after discharge and seven while still under observation in this hospital. Table II shows the roentgenologic and pathologic observations on these thirteen patients. Four had bronchopleural fistulae, three recurring disease in the same area, five segmental plane cavities with bronchiectatic communication, and one source was not determined. Planigrams in twelve patients revealed bronchiectasis in six instances. Bronchograms in ten patients revealed bronchiectasis in eight. Nine of the thirteen patients had further resections. Pathologic findings are summarized in Table II. All had bronchiectasis demonstrated either on x-ray or in the pathologic specimen. Capel and Mitchell [*28*] believe that tubercle bacilli left in the damaged area of resection and inadequate chemotherapy were probably the causes of their patients' relapses. Bell [*29*] considers resistant organisms to be the most likely factor in his patients' relapses. Our data, based on careful x-ray studies and pathologic sections, would seem to indicate that tuberculous bronchiectasis may be the important factor in causing relapse or continuing positive bacteriology.

TABLE II
OBSERVATIONS ON 13 PATIENTS WITH POSITIVE SECRETIONS FOLLOWING SURGERY

Observations	No. Patients
X-ray diagnosis:	
Bronchopleural fistula	4
Recurring disease in same area	3
Segmental plane cavity	5
Source not determined	1
Roentgenologic evidence of bronchiectasis:	
Posteroanterior roentgenograms (13)	1
Planigrams (12)	6
Bronchograms (10)	8
Pathology of nine specimens resected for relapse:	
Fibrocaseous	9
Bronchiectasis	8
Segmental plane cavity	4
Bronchopleural fistula	2

CASE VIII. M. A. was selected to show a typical example of a new cavity forming in a segmental plane with a bronchiectatic communication. He also demonstrated the importance of obtaining preoperative planigrams and bronchograms, which were not

requested. The presence of a persistent cavity should arouse one's suspicion of accompanying bronchiectasis. This patient is a twenty-two year old white man with moderately advanced disease and a large, thick-walled cavity. The condition was discovered in the Army in June, 1954, following a motorcycle accident. Sputum and gastric cultures were negative. Tuberculin skin test was positive. Treatment consisting of streptomycin and para-aminosalicylic acid was initiated at that time. The preoperative x-ray (Fig. 11) revealed the persistent thick-walled cavity. On December 16, 1954, a segmental resection of the left upper lobe was completed. The surgeon noted a fibrotic and thickened segmental bronchus which he was able to mobilize and transect. Organisms recovered from the specimen were resistant to streptomycin and para-aminosalicylic acid. Pathologic sections revealed the cavity without demonstrable bronchial communication. The immediate postoperative course was uneventful. Two months after operation he began producing bloody sputum which was positive for acid fast bacilli. Planigrams and bronchograms (Fig. 12) revealed a cavity in the area of operation with dilated bronchial communication. On May 26, 1955, the remaining portion of the left upper lobe was removed. Figure 13 shows the ragged cavity in the scarred area of the previous resection.

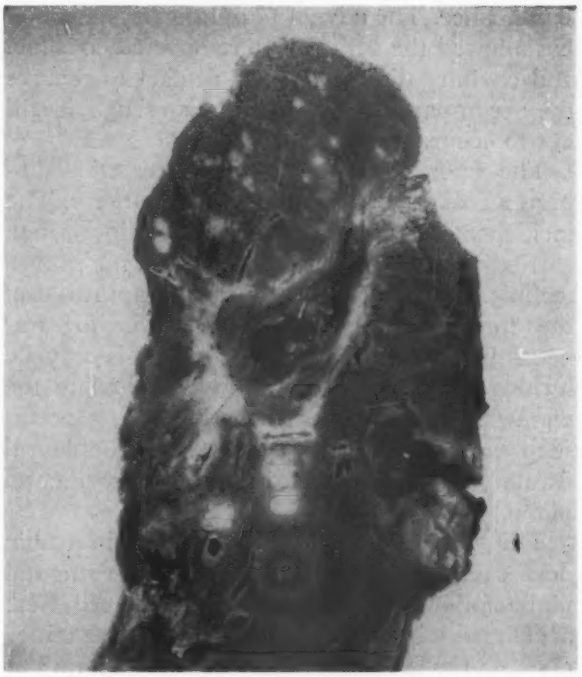

FIG. 13. M. A., a twenty-three year old man. Pathologic section through left upper lobe showing ragged cavity in intersegmental plane and dilated, thick-walled bronchus which communicated with cavity.

The three other cases were quite similar and another patient, not in this series, was resected secondarily for hemorrhage without positive secretion. He also had a ragged cavity in the segmental plane with two large bronchial communications.

COMMENTS

The x-ray characteristics of bronchiectasis have been well described [*30*]. The pathologic features of bronchiectasis are less well defined particularly when slight to moderate degrees of ectasia are present. It is in these latter areas that there is poor correlation between x-ray findings and pathologic diagnosis. It is not unusual to find good x-ray evidence of bronchiectasis only to be disappointed by the pathologic report of no bronchial disease. Comparison of the x-rays with the pathology at lung cutting has greatly increased the pathologist's awareness of bronchiectasis. Two inherent difficulties are apparent: (1) Fixing fluids tend to shrink lung tissue and contract the bronchi. Inflation of the lung with fixing fluid under pressure partially overcomes this tendency to collapse and shrinkage. (2) There are no standard pathologic criteria for the diagnosis and grading of various degrees of bronchiectasis. Casts of bronchi utilizing plastic material will beautifully demonstrate the degree of bronchiectasis. Unfortunately, the process of digesting the lung away from the cast destroys the lung tissue so that no search can be made for evidence of tuberculous involvement. It would appear feasible to fill the bronchi with plastic material and then sacrifice a portion of lung tissue for section, retaining the remainder for digestion to obtain an almost complete bronchial cast. We are not aware, however, of any such definitive combined study. Nevertheless, the evidence presented in this paper supports the concept of tuberculous bronchiectasis.

Astute phthisiologists even in the days of pneumothorax and primary thoracoplasty were aware of the hazards of bronchiectasis. In the present era of chemotherapy and pulmonary resection, bronchiectasis in the presence of tuberculosis has been largely neglected. Physicians are aware that large caseous foci and persistent cavities are difficult to eradicate. These may contribute to long continued positivity of sputum and to development of organisms resistant to the antibiotic drugs. It seems evident that bronchiectasis should be considered as a possible additional factor. Indeed large caseous foci, cavitary disease and bronchiectasis are so closely allied in the pathology of tuberculosis of the lung that it has been difficult to separate their true

significance. The advent of pulmonary resection has allowed the surgeons to remove caseous foci and cavitary disease. If they neglect to remove the accompanying bronchiectasis relapse is still apt to occur.

The operation for segmental resection has been a real advance in pulmonary surgery. The incidence of complications is very low when carried out by surgeons familiar with the proper technic. The importance of careful appraisal of the lung by planigrams and bronchograms needs further emphasis. Bronchiectasis may be lurking in a neighboring segment close to the segmental plane. Inadvertently cutting across such an area may lead to bronchopleural fistula or cavity formation in the segmental plane.

This paper describes five patients in whom new cavities developed within the segmental plane following segmental resection. All were associated with ectatic bronchi which remained open or reopened following the operation. The cavity seems to develop within the lung in the segmental plane when the pleural continuity has been re-established and adhesions obliterating the pleural space have developed in the operative area, thus preventing the establishment of a true bronchopleural fistula.

SUMMARY

1. The concepts of the pathogenesis of tuberculous bronchiectasis are discussed.

2. Tuberculous endobronchitis associated with bronchiectasis is a cause of recurring hemoptysis and positive sputum, especially after respiratory infections.

3. Dense fibrosis in bronchiectatic areas may sequester tubercle bacilli which may not be eradicated or modified by chemotherapeutic agents.

4. Tuberculous bronchiectasis was an important cause for failures in pneumothorax treatment and primary thoracoplasties.

5. Segmental resection is now an accepted surgical procedure. Careful appraisal of the involved lobe by planigrams and bronchograms is indicated prior to segmental resection in order to avoid complications associated with the type of tuberculous bronchiectasis which approaches dangerously near the intersegmental plane of dissection.

6. Five patients are reported in whom new cavitary disease with communicating dilated bronchi developed in the segmental plane of a previous segmental resection. Four were associated with bacteriologic relapse and one was resected because of hemorrhage.

Acknowledgment: Dr. James M. Wilkie kindly allowed me to report Case 1 and Dr. Walter H. Jaeschke supplied the microscopic section.

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Accuracy of the Confirmatory Diagnosis of Tuberculosis*

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THERE are many excellent articles in the literature that outline the fundamental procedures necessary to confirm the diagnosis of tuberculosis after the disease has been suspected by routine posteroanterior roentgenograph [*8,38,62*]. The accuracy of these procedures in a large series of cases has not been reported, nor has the extent of disease been correlated with these procedures. Such a study, of 1,295 consecutive admissions to the Central Washington Tuberculosis Hospital with x-ray changes, therefore was undertaken. These admissions cover the five-year period from January 20, 1950 through December 31, 1954. A proved diagnosis of active tuberculosis was established in 629 cases either by the recovery of tubercle bacilli or by pathologic examination of tissue. The patients represent all age groups, both sexes and all types of tuberculosis; primary and reinfection, pulmonary and extrapulmonary.

Yerushalmy [*65–67*] and Newell et al. [*43*] pointed out the great inherent error in interpretation of routine posteroanterior roentgenographs. This liability to error makes confirmation of a diagnosis in chest disease imperative if resection is to be performed on patients with bronchogenic carcinoma with as little delay as possible and if the patients with tuberculosis are to be treated before the disease spreads and before they infect others. The discovery of new drugs and new technics in the treatment of patients with tuberculosis which yield better results in one-third the time previously required, together with the continued high incidence of the disease [*2,3,19,21,63*] as indicated by the discovery of many cases through x-ray surveys, make necessary an evaluation of the reliability of the methods employed to establish this diagnosis.

The confirmatory diagnosis of tuberculosis is based upon a positive skin test, recovery of tubercle bacilli from sputum, gastric content, discharging material from fistula, pleural effusion, urine and tissue pathology. Because the erythrocyte sedimentation rate is supposed to have a high correlation with active disease, the results of a study of the sedimentation rate in this connection are also reported.

For many years the skin test was discredited because in over 70 per cent of the children tested a positive reaction developed by the time they were fourteen years old [*52*] and because reports from large city morgues showed that primary tuberculosis was found in 90 per cent or more of autopsies [*34*]. The results of recent skin testing of children by Myers et al. [*41*] in 1954 gave a very different result, for only 3.9 per cent of the skin tests were positive. Testing of 5,304 student nurses between 1930 and 1954 revealed that 15.2 per cent of the skin tests were positive when they entered training and another 22.7 per cent converted while in training for a total of 37.9 per cent positive skin tests on graduation [*39*]. In testing medical students Myers et al. [*40*] found that in the class of 1936, reactions were positive in 62.8 per cent of the students when they graduated and 47 per cent of these had converted during medical school; in the class of 1951, however, reactions were still negative in 62.8 per cent when they graduated.

In a tuberculin survey made by the health department in a chest clinic in metropolitan New York, using 1–1000 O.T., it was found that the positive reactors varied from a low of 18 per cent in the one to fourteen year old group to a high of 82 per cent in the forty-five to sixty-four year old group [*51*]. In our chest clinics, in which over 600 suspects from the mass x-ray surveys in Benton-Franklin, Grant and Klickitat counties were skin tested, using 1–1000 O.T., the age group from six to eighteen had 12.2 per cent

* From the Central Washington Tuberculosis Hospital, Selah, Washington.

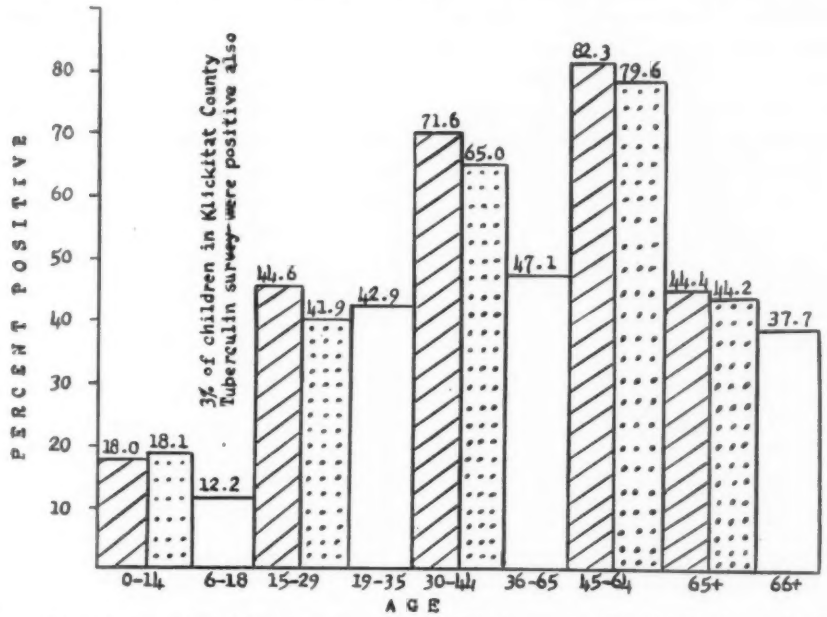

FIG. 1. Comparison of incidence of positive reactors in New York survey (hatched columns) with authors' survey (dotted and open columns).

positive reactors, age nineteen to thirty-five had 42.9 per cent positive reactors, age thirty-six to sixty-five had 47.1 per cent positive reactors and those sixty-five and over had 37.7 per cent positive reactors. Figure 1 shows a bar graph comparing the incidence of our positive reactors with that from the New York survey. When 3,276 children in Klickitat County were skin tested reactions were positive in 3 per cent, but in the six to eighteen year group picked up in our survey reactions were positive in 12.2 per cent, more than twice the usual incidence. In both our surveys and that conducted in New York, the sixty-five year and older group had a lower incidence of positive skin tests than the groups from thirty-six to sixty-five. It has been suggested that this might be due to a decrease of skin sensitivity in the older age group. Of these survey patients with x-ray changes suggestive of tuberculosis, the over-all percentage of positive skin tests was 41 per cent, so 59 per cent of this group could be eliminated as tuberculosis suspects on the basis of a negative skin test if the results of Sweany [*58*], Musac chio [*37*] and Douglas [*17*] are valid, since they found that the absence of a positive skin test rules out tuberculosis in 97 per cent of cases. In the past, too much emphasis has been placed upon the 3 per cent that are exceptions to the rule: this group is comprised chiefly of (1) children in whom tuberculosis is developing but who have not had the forty-two to 120 days necessary to develop a positive skin test, and (2) moribund patients in whom diagnosis can usually be made by positive sputum findings if the sputum is examined.

The errors in skin testing are: (1) use of outdated material; (2) failure to refrigerate the material after mixing; (3) use of a too dilute solution (less than 1–1000 O.T.); and (4) not injecting the material intradermally. We have seen no sloughing from this concentration in the seven years that we have used it in health department clinics. Reading of the test is simple: any redness or induration over 5 mm. in diameter after forty-eight hours is positive. A positive skin test in a child under five years of age is indicative of active primary disease [*31,48,49*]. A positive Mantoux test in persons over this age indicates that they have had primary infections and active tuberculosis must be ruled out if they have any disease.

Table 1 represents a summary of the culture results over the last five years of both outpatient and inpatient specimens.

It has been stressed by other authors that if tubercle bacilli are to be recovered, repeated and adequate sputum specimens must be collected after eliminating as many mouth organisms, yeasts and saprophytes as possible, preferably after brushing the teeth and rinsing the mouth [*7*]. Since to obtain a positive result in sputum on direct smear requires at least 100,000 organisms per cc. [*56,64*] of sputum, this procedure is rarely used. Instead, the specimen is

digested with 4 per cent NaOH solution, shaken for ten minutes, incubated for two to three hours and shaken again, if necessary, to emulsify. It is then centrifuged for twenty minutes at 3,300 r.p.m. The supernatant fluid is poured off and the sediment is then neutralized with 4 per cent volume for volume hydrochloric acid. This sediment is smeared and stained with Ziehl-Neelsen stain and scanned under a high power oil immersion microscope. Eight hundred and five positive smears of both inpatient and outpatient's sputums are reported in 274 patients.

TABLE I
SUMMARY OF CULTURES
CENTRAL WASHINGTON TUBERCULOSIS HOSPITAL
1950 THROUGH 1954

Result	Lowenstein Medium		Petragnani Medium	
	Cultures (no.)	Percentage	Cultures (no.)	Percentage
Inpatient Cultures				
Positive	1,404	16.2	1,596	17.2
Confirmed	1,178	13.5	1,191	12.8
Negative	6,119	70.3	6,486	70.0
Total	8,701	....	9,273	....
Outpatient Cultures				
Positive	174	5.0	181	5.0
Confirmed	573	17.0	587	17.0
Negative	2,635	78.0	2,764	78.0
Total	3,382	....	3,532	....
Total Inpatient and Outpatient Cultures				
Positive	1,578	13.2	1,777	13.9
Confirmed	1,751	14.5	1,778	13.9
Negative	8,854	73.3	9,250	72.2
Total	12,083	....	12,805	....

The sediment is also cultured on a tube each of Jensen and Holm's modification of Lowenstein's media [*36,54*] and Petragnani's media using pour technic. There were twelve patients during these five years who had a positive sputum on smear, without growth of the rest of the sediment on either culture media. Two of the twelve had positive cultures at other institutions, four had tuberculosis at tissue examination, and six had only x-ray evidence of tuberculosis.

How is it possible to get a positive sputum on smear and a negative result by culture? First, the result of the smear examination could be a false positive, as seen in fifteen patients who were admitted with no evidence of tuberculosis but with reports of a positive smear from other laboratories. Similar experiences have been reported by Steinberg et al. [*57*]. In our fifteen cases pyorrhea was the most common cause of this error. Because of the presence of other acid-fast rods in the gastric content and the low incidence of positive smears [*35,50*], gastric specimens are not smeared. Second, all digestant materials kill 80 per cent or more of the viable tubercle bacilli, although sodium hydroxide seems to be the least lethal of all digestant materials used today [*22,44*]. In our experience 38.8 per cent of patients with positive sputum cultures gave positive results for smears of the sputum concentrate.

During the five year period 8,701 inpatient specimens were cultured—1,404 were positive, 1,178 were contaminated and the balance of 6,119 were negative. Of 9,273 cultured on Petragnani's media, 1,596 were positive, 1,191 were contaminated and the balance of 6,486 were negative. Culture medium is prepared fresh at least every two weeks and stored in a refrigerator at 37.5°F. until used. Positive and negative control tests are carried out on each batch of medium and it is used within a two-week period. Only strictly fresh eggs are used because, as has been stressed by others [*9,29*], the use of even two-week old eggs decreases the sensitivity of media. Old media lose sensitivity after a few weeks even though stored in a refrigerator in air-tight containers. After inoculation, the tubes are placed in an incubator in a horizontal position for twenty-four hours, then upright. Visible colonies appear in twelve to twenty-eight days (average twenty-one days). Negative cultures are discarded at six weeks. Longer incubation was not possible because of the large volume of cultures, and a small percentage of positive results may therefore have been missed [*26*]. One guinea pig inoculation will give positive results in 80 per cent of patients known to have tuberculosis and one culture gives 75 per cent positive results in these circumstances, so the two methods are about equally reliable and may be considered to be complementary [*1,18,23,25,28,47,53*]. However, the technical

ease of the culture procedure makes this superior to guinea pig inoculation when the total number is very large.

Our results show Petragnani's media to be slightly more sensitive than Lowenstein's both for inpatients and outpatients: 17.2 per cent positive results in inpatients using Petragnani's media, as compared with 16.2 per cent positive results for the same group of patients using Lowenstein's media. Both gave 5 per cent positive results in outpatients. This is the reverse of the results Melvin et al. [*36*] obtained when 1,885 specimens were compared. The use of the two media is complementary, as shown by those patients with a single positive culture. During the five-year period 127 patients had only one positive specimen, fifty-two were positive on both Petragnani's and Lowenstein's media, thirty-seven were positive only on Petragnani's media, and thirty-eight were positive only on Lowenstein's media. Tissue obtained by resection or autopsy was available in twenty patients. The diagnosis of tuberculosis was substantiated in fourteen cases and in six cases the pathologic report differed from the culture: one was a coccidioma, one a non-specific lung abscess, one fibrosing pneumonitis, two bronchiectasis and one emphysema. However, as will be discussed later, the accuracy of tissue diagnosis is not as high as one might assume. Thus a patient with a single positive result either on smear or culture must be considered to have active tuberculosis and should be treated accordingly.

Contamination is a real hazard in culture work. All the cultures were checked according to media to see whether or not both were contaminated and to see which specimens were most commonly contaminated. Lowenstein's medium was contaminated more commonly, both in inpatient and outpatient cultures: 13.5 per cent contaminated in inpatients, 17 per cent in outpatients. Using Petragnani's medium, 12.8 per cent were contaminated in inpatients and 17 per cent in outpatients. Those specimens most often contaminated are draining sinuses, aspirated chest fluid, joint fluid, spinal fluid and urine. Outpatient sputums showed 14 per cent contamination using Petragnani's medium and 16 per cent using Lowenstein's medium. Twelve per cent of gastric cultures were contaminated on Petragnani's medium and 13 per cent on Lowenstein's medium. Inpatient sputums had the lowest incidence of contamination, 8.4 per cent. Only 5 per cent of patients gave contaminated cultures on both media, and Feld [*20*] reported that he had a lower contamination rate when three culture tubes were used. Variation in temperature of the specimen above or below 30°c. causes a rapid fall in the number of positive cultures to be expected. Gastric culture is more reliable than sputum culture and is possible when sputum is not made available by the patient [*27*]; more than one gastric culture is recommended. Since the tubercle bacillus is susceptible to changes in pH, it is to be expected that the number of positive cultures obtained after the bacilli have resided a few hours in the acid content of the stomach would decrease the efficiency of gastric culture (it is estimated by 32 to 42 per cent) so that mailing gastric content for culture without first buffering it makes this test useless [*33*]. This pH factor must be taken into account also in urine; moreover several urinary by-products of the metabolism of vitamin C are bactericidal [*42*]. Another complicating factor is the use of almost any antibiotic which inhibits the growth of tubercle bacilli, such as terramycin, streptomycin and isonicotinic acid hydrazid. Mailing sputum specimens in hot weather frequently results in death of most of the tubercle bacilli as well as increase in the overgrowth of contaminants, thus accounting for the lower number of positive results in outpatient cultures and the higher number of contaminations. When one realizes the difficulties in recovering tubercle bacilli and knows where these procedures can go wrong, the value of short term study by obtaining three gastric specimens that can be cultured immediately by qualified technicians using culture media that grow tubercle bacilli, becomes of increasing importance. If the bacilli are dead on arrival or viable tubercle bacilli are planted on culture media that will not support them, negative results, of course mean nothing.

Sweany [*59*] reported that 85 per cent of patients admitted from 1935 to 1941 gave positive sputum results on smear, another 5 per cent by animal inoculation, and 2.7 per cent more by culture of gastric content. Medlar [*35*] reported that tubercle bacilli could be recovered from almost all patients in a tuberculous institution. Our results agree with neither of these reports. Because of the difficulties in recovering tubercle bacilli, patients with x-ray changes that might be active tuberculous disease have been admitted to the hospital for work-up which includes: (1) routine posteroanterior chest roentgenographs,

TABLE II

TYPE OF TUBERCULOSIS

	Primary	Extra Pulmonary	Minimal	Moderately Advanced	Far Advanced	Total Cases
Sputum:						
Smear	0	0	0	63	134	197
Culture	0	2	21	83	91	197
Positive:						
Gastric I	14	5	18	44	28	109
Gastric II	5	2	9	20	9	45
Gastric III	3	1	4	14	9	31
Other aspirated material	0	14	1	0	1	16
Pathology	0	12	0	9	13	34
Total	22	36	53	233	285	629
Total pathology	0	19	1	64	105	189
Normal sedimentation rates	9	8	22	66	62	167
Percentage of total	40	21	41	28	21	26.5

the extent of the disease being classified according to N. T. A.* Diagnostic Standards (1950); (2) sedimentation rate; and (3) sputum, if any, from which a concentrate is prepared, smeared and cultured. If this smear is positive, then a second sputum specimen is collected on the following day, if the smear is negative, then a gastric specimen, obtained with the patient fasting, is tested on three consecutive days by culturing on one tube each of Lowenstein's and Petragnani's media. One thousand two hundred and ninety-five patients have been studied this way, 274 patients have had positive sputum results on smear; however, only 197 completed their treatment at this institution and the balance, seventy-seven, were transferred to Veterans hospitals or other facilities in the state (this group of seventy-seven is not considered in our discussion of the accuracy of pathologc diagnosis). Another 197 patients gave positive results with sputum culture but were negative on smear. One hundred nine patients gave positive results with the first gastric specimen culture, in forty-five more results were not positive until the second culture was obtained and in thirty-one on the third attempt. Sixteen patients gave positive results on culture of urine, spinal fluid and sinus tract drainage, and in thirty-four patients results were positive only by tissue examination. The 629 patients that were treated here were divided into five categories: twenty-two patients had primary tuberculosis, thirty-six had extra-pulmonary tuberculosis, fifty-three had minimal pulmonary tuberculosis, 233 had moderately advanced and 285 had far advanced pulmonary disease.

In the vertical column on the left of Table II the tests are listed in order of sensitivity, starting with positive results on sputum smear, sputum culture, first gastric examination, second and third gastric examination, positive results on aspirated material (such as urine and spinal fluid) and, lastly, positive findings only on tissue examination. Those results listed as positive on smear were usually positive on culture of that sputum, with exceptions already discussed. Those results positive on gastric culture were positive only on gastric culture, and it is obvious that the first culture gave the highest number of positives, yet the second and third gastric content examinations were positive in seventy-six patients. After all these efforts to culture tubercle bacilli, thirty-four patients gave evidence of tuberculosis only on tissue examination. However, direct tissue examination was performed in 189 patients of the total of 629.

On the bottom two lines of Table II are figures showing the number of patients with a proved diagnosis of active tuberculosis who had erythrocyte sedimentation rates of 15 mm. per hour or less by the Wintrobe method, and the percentage of patients in each group (according to extent

*National Tuberculosis Association.

of disease) who had normal sedimentation rates. The poorest correlation is found in the minimal and primary tuberculosis groups, 41 per cent and 40 per cent having normal rates. The best correlation is found in extrapulmonary and far advanced tuberculous disease, yet even here 21 per cent of the patients have normal sedimentation rates [*6,60*], patients with moderately advanced tuberculous disease fall between these two extremes, with 28 per cent having normal sedimentation rates. Of all 629 cases, 167 had normal sedimentation rates, representing 26.5 per cent of the total. In view of this poor degree of correlation with activity, erythrocyte sedimentation rates probably only confuse the issue.

Table III shows the pathologic diagnoses other than tuberculosis that have been made in 189 patients in whom tissue examination was available including 150 surgical resections and 39 autopsies. Why should the results of tissue examination and the presence of positive cultures disagree in over 15 per cent of the cases? First, in the diagnosis of bronchiectasis, if tuberculosis is a secondary invader of a congenital lesion as thought by Medlar [*34*], the diagnosis of tuberculosis can be missed easily unless serial sections are made, and even with this technic the diagnosis of bronchiectasis was made in 8 per cent of the surgical specimens even though positive cultures were obtained before resection. This may explain why in 7 per cent of patients resected for bronchiectasis before the advent of antituberculous chemotherapy clinical tuberculosis developed later on follow-up. Of our seven patients with bronchiectasis, all had had at least one positive culture and five had had repeated positive cultures, so our results parallel Medlar's series. Two of the three patients listed in Table III considered by the pathologist to have inactive tuberculosis had repeated positive cultures (one died of tuberculous meningitis and another of bronchogenic carcinoma, yet both patients had positive cultures within six weeks of the time of death); thus the pathologist may not be able to determine whether or not active disease is present. The patient with coccidioma had typical tubercle formation, with spherules visible both on hematoxylin-eosin stain and Schiff's stain; only one positive culture had been obtained in this patient, which might have been due to laboratory error. However, since the two diseases are commonly associated, it would be impossible to rule out tuberculosis on the basis of the pathologic findings alone. Both patients with atypical granulomatous pneumonitis had repeatedly positive cultures, as did two of the three patients with fibrosing pneumonitis, both patients with granulomatous bronchitis, the two patients with anthrosilicosis, four of the seven patients with fibrosis, and one of the two patients with emphysema; yet in all the eighteen patients in whom resection was performed cultures were negative after surgery. The one patient with chronic epididymitis had repeatedly positive gastric cultures (from his pulmonary lesion) and clinically the epididymitis fitted into the picture of tuberculosis; nevertheless the pathologist could not find typical changes of tuberculosis. Why, then, is a diagnosis of nontuberculous disease made in these patients, in the face of clinically active tuberculosis with repeatedly positive cultures? There are two possible answers: first, as Medlar suggested, the pathologist may see these lesions early in the evolution of typical tubercle formation, before the classic picture develops, and second, the pathology of tuberculosis is altered by combined drug therapy [*4,5,11–16,46,61*]. Most pulmonary resections have been performed since June 1, 1952 when we began the continuous and concurrent use of PAS, streptomycin and isoniazid, with early resection after three to four months of combined drug therapy.

TABLE III
PATHOLOGIC DIAGNOSIS OTHER THAN TUBERCULOSIS
PATHOLOGY—189 PATIENTS
(Surgical Resection—150)
(Autopsy—39)

Diagnosis	Number
Bronchiectasis	7
Atypical granulomatous pneumonitis	2
Fibrosing pneumonitis	3
Granulomatous bronchitis	2
Anthracosilicosis	2
Emphysema	2
Inactive tuberculosis	3
Fibrosis	7
Chronic epididymitis—no evidence of tuberculosis	1
Coccidioma	1
Total	30 (15.8%)

COMMENTS

The Mantoux test, starting with a dilution of 1–1,000 and increasing to 1–100 O.T., has an

accuracy of 95 per cent or over in ruling out tuberculosis. Since such a large percentage of our population has negative skin tests, the use of the Mantoux reaction gives us a sharper diagnostic tool than we have in almost any other test in medicine. We need only bear in mind the two common exceptions which are, first, the moribund patient whose sputum is positive for acid-fast bacilli on smear; and second, and most common in our experience, the child with recent contact and a negative skin test at first follow up, who, six weeks later, may have not only a positive skin test but also pneumonic disease evident on x-ray.

During the five-year period covered by this report we have treated ninety-eight patients with primary disease who have shown both a positive skin test and x-ray evidence of pneumonic disease. Of these, twenty-two patients had one or more positive gastric specimens; thus tubercle bacilli were recovered from 22.6 per cent of this entire group (fourteen positive on the first gastric examination, five on the second, and three on the third). The twenty-two patients from whom tubercle bacilli were recovered are the only cases with a substantiated diagnosis and are part of the total of 629. None of this group with primary disease died, hence direct confirmation is not available; 40 per cent had normal sedimentation rates. These results are similar to those reported in patients with recent skin test conversion [*55*].

Extrapulmonary tuberculosis develops as a result of spread, usually via the blood stream to areas outside the lung, yet of the thirty-six patients in this group it was possible to obtain positive cultures of sputum in two instances, positive gastric cultures in eight more, positive cultures of other material (such as aspirated fluid, urine and spinal fluid) in fourteen additional subjects, and tissue confirmation in twelve. There was a better correlation between erythrocyte sedimentation rate and degree of activity in this group, but even here 21 per cent had normal sedimentation rates. Even with all the new drugs available in the treatment of tuberculosis today, we have lost 16 per cent of our children under five years of age as a result of the development of tuberculous meningitis. It is frequently not possible to recover tubercle bacilli either from the spinal fluid or gastric culture of these children, and the diagnosis consequently is not proved until autopsy. However, a presumptive diagnosis should be made and treatment started on the basis of the following manifestations: (1) a child with meningeal irritation, (2) positive Mantoux test, (3) spinal fluid changes consisting of a fall in sugar, rise in cell count becoming predominantly lymphocytes, rise in protein, and, particularly important, pellicle formation.

A large percentage of patients with tuberculosis of bone can be accurately diagnosed. We recommend biopsy of all peripheral lesions and, in view of the high incidence of other system disease (81 per cent among our cases) confirmation of the diagnosis frequently can be made by gastric, urine or sputum culture [*24,32*]. The first drainage from sinus tracts is usually positive for tubercle bacilli on smear and culture but after they have drained for a time the culture is seldom positive and has the highest incidence of contamination of all the materials cultured for tubercle bacilli. Typical spine lesions in roentgenograms combined with a positive Mantoux test affords accurate diagnosis in 88 per cent of patients when an established diagnosis was made by direct attack upon the body of the vertebra [*30*]. The diagnosis of tuberculosis peritonitis or tuberculous adenitis, in our experience, is exclusively a pathologic diagnosis. We have not had a large enough series of cases of renal tuberculosis to be able to evaluate the accuracy of culture. It is difficult to grow tubercle bacilli from urine if the pH is much above or below 7.0; another complicating factor is that several by-products of the metabolism of vitamin C are bactericidal. Our greatest difficulty in diagnosis is that these patients frequently have received antibiotics such as terramycin or streptomycin, which inhibit the growth of tubercle bacilli in culture media, before the urines are sent to our laboratory to be cultured.

By N. T. A. classification of pulmonary tuberculosis, any lesion containing a cavity visible on routine posteroanterior x-ray should be interpreted to indicate moderately or far-advanced tuberculosis, depending upon the size of the cavity or total size of all the cavities present. The presence of a positive sputum on smear is usually associated with a cavity which has direct communication with a bronchus. No patient with minimal disease had a positive sputum on smear, and only twenty-one of the fifty-three patients with proved minimal tuberculosis had positive sputum cultures. These results are comparable to those reported by others [*10,45*]. The diagnosis in thirty-one cases was proved by three gastric

cultures, and one was established by culture of material aspirated at the time of bronchoscopy. There were no resections and no deaths in this group. The erythrocyte sedimentation rate showed the poorest correlation with activity, 41 per cent. There were 134 patients with a positive Mantoux test and x-ray changes that could be minimal tuberculosis, and only eight of this entire group had three negative gastric cultures but came back later with a proved diagnosis of tuberculosis; an error of 6 per cent.

In respect to patients with moderately advanced disease, we had sixty-three with positive sputum on smear, eighty-three with positive sputum on culture, seventy-eight with positive gastric cultures, and nine in whom the diagnosis could not be proved until the pathologic findings were available. There were no tuberculosis deaths in these moderately advanced cases; however, three died of associated diseases (the remaining tissue diagnoses came from resected material). During the five-year period 464 patients were admitted with a positive Mantoux test and x-ray changes extensive enough to be classified as moderately advanced disease; only nine patients had three gastric cultures that were negative and later came back with a proved diagnosis of tuberculosis, an error of less than 2 per cent. The correlation of erythrocyte sedimentation rate with activity was 72 per cent (28 per cent had normal sedimentation rates).

The patients with far-advanced disease fit better into the accepted pattern of diagnosis, 225 of the 285 giving positive results on sputum smear or culture, but it must be stressed that many of these patients had three or more outpatient sputum specimens examined before the positive smear or culture was obtained; in forty-six results were positive on gastric culture. But even here, with all the culture work that was done, a diagnosis was not established in thirteen patients until they were resected or examined at autopsy. A total of 325 patients were admitted with x-ray changes consistent with far-advanced tuberculosis; of these three had negative results after three gastric cultures and later came back with a proved diagnosis of tuberculosis. Thus many samples are required to establish a diagnosis of tuberculosis even though the disease may be extensive.

If the number of diagnoses established only by pathologic examination in the moderately and far-advanced cases is added to those missed after the first three gastric cultures—nine plus nine cases of moderately advanced tuberculosis and thirteen plus three cases of far-advanced disease—this total represents 5 per cent of all cases that could not be diagnosed by sputum smear and culture and gastric culture. This error is very similar to the 6 per cent error reported in minimal disease. It would appear from this result that in the reinfection type of pulmonary disease, culture can be almost as accurate in minimal as in moderately or far-advanced tuberculosis.

SUMMARY

1. The accuracy of the properly performed tuberculin skin test beginning with 1–1000 O.T. and followed by 1–100 O.T.), if negative with both dilutions, is so great in ruling out tuberculosis that it becomes the keystone in the diagnosis of the disease, since 59 per cent of patients even with roentgenographic changes sufficient (in miniature films) to arouse suspicion of tuberculosis have negative Mantoux tests.

2. A positive Mantoux test in a child less than six years of age indicates active primary disease. A positive Mantoux test in a patient over six years of age indicates a prior primary infection, and if disease is present anywhere in the body, tuberculosis must be ruled out.

3. In order to recover tubercle bacilli from lesions, repeated specimens cultured on two different media are required because the tubercle bacilli may not be present in sputum or gastric cultures every day and may grow better in one medium than another even though both will support tubercle bacilli in the positive control.

4. Lowenstein's and Petragnani's media are complementary and equally effective in outpatient cultures. Petragnani's medium gives a higher percentage of positive results on inpatient cultures and a lower percentage of contaminations.

5. A single positive smear or culture is sufficient reason to hospitalize a patient and to begin treatment.

6. Many factors influence the recovery of tubercule bacilli: (a) total number of tubercle bacilli in the specimen; (b) the digestant material kills 80 per cent of the viable tubercle bacilli; (c) pH above or below 7 may rapidly kill the tubercle bacilli; (d) temperature changes of specimens above or below 30°c. decrease the number of viable tubercle bacilli; (e) by-products of vitamin C in urine are bactericidal; and (f) antibiotics inhibit the growth of tubercle bacilli on culture media.

7. Contamination is a major problem in culture work, the highest contamination occurring in outpatient specimens, drainage from sinus tracts, and aspirated fluids. The lowest contamination rate occurs with inpatient sputums.

8. Using three specimens cultured on two different media, we have recovered tubercle bacilli from 22.5 per cent of primary cases, 94 per cent of patients with minimal tuberculosis, 95 per cent of patients with moderately advanced pulmonary tuberculosis, and 95 per cent of patients with far-advanced tuberculosis.

9. The erythrocyte sedimentation rate is of no value in the diagnosis of active tuberculosis since we found it to be normal in over one-fourth of patients with positive cultures.

10. A pathologic diagnosis of tuberculosis was not returned in thirty of 189 specimens sent even though one or more positive cultures had been obtained from each patient. There was disagreement between culture and pathologic diagnosis in 15.8 per cent of these cases.

11. Since the advent of combined chemotherapy all our tuberculosis deaths occurred in patients with advanced disease, either pulmonary or extrapulmonary, which was present on admission; there were no deaths from primary or minimal pulmonary disease.

12. When one realizes the difficulties in recovering tubercle bacilli and the ways in which these procedures can go amiss, the value of short-term work-up with three gastric specimens that can be cultured immediately by qualified technicians using culture media that grow tubercle bacilli, becomes of increasing importance. If the bacilli are dead on arrival, or viable tubercle bacilli are planted on culture media that will not support them, negative results mean nothing.

13. Without the three-day period of hospitalization during which three gastric specimens are cultured, the diagnosis would have been missed on one-third of the total group; early disease, minimal and moderately advanced pulmonary and primary disease would have been missed most commonly.

14. Tissue examination is of great value in the diagnosis of tuberculosis in extrapulmonary lesions since one-third of this group were diagnosed on the basis of pathology reports; it is of less value in diagnosing moderately and far-advanced disease and of no value in minimal and primary disease since these patients do not require resection nor do they die of the disease.

15. Active tuberculosis is a clinical and not a pathologic diagnosis and it is best substantiated by the recovery of tubercle bacilli from the lesion.

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Reviews

Brucellosis in Egypt*

A Review of Experience with 228 Patients

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OVER the past six years 228 patients with bacteriologically proved brucellosis have been studied at this Unit.† The program has been operated by the NAMRU staff‡ with the support and encouragement of the Egyptian Ministry of Public Health and the cooperation of the Ministry Fever Hospitals. Previous reports [*1–9*] have covered various parts of the study, with emphasis on therapeutic results. Since there has been no detailed compilation of our total experience by which we can compare the disease as seen in Egypt with that reported from other areas, we have undertaken this review.

CLINICAL DATA

Selection of Cases. The patients in this study were selected at Egyptian Government Fever Hospitals in the Cairo area on the basis of two criteria: (1) a history suggestive of brucellosis, and (2) a brucella agglutination titre above 1–160. These patients were transferred to this Unit for further evaluation through the kindness of the Directors of these hospitals. Relatives of patients with a suggestive history were investigated and if they met these criteria they also were admitted. No patient is reported upon in this study who did not have a positive brucella blood culture.

Age: The mean age of these patients was thirty-two years, the youngest was nine years of age and the oldest was aged seventy. One hundred and thirty one patients (57 per cent) were in the age group between twenty-one and forty years. The different age groups are shown in Table 1.

Sex: There were 219 males and nine females. There were no convenient facilities for female patients until recently, and therefore only a limited number have been admitted for study. The actual incidence of brucellosis in the two sexes could not therefore be determined under these circumstances.

Residence: The design of the study was directed towards obtaining as many brucella patients as possible, and no conclusions can be drawn concerning geographic distribution or other epidemiologic aspects.

Occupation: These 228 patients were divided into the following groups: 105 were tradesmen, sixty-one were farmers, twenty-four were laborers, ten were well-to-do persons without a trade, six were animal handlers and three were housewives. In nineteen cases the occupation was not recorded.

Possible source of infection: The information obtained in this clinical study was unsatisfactory for making valid suggestions as to the probable source and mode of infection. The majority of the patients had daily intimate contact with

† NAMRU-3 is the United States Naval Medical Research Unit at Cairo, Egypt, established in 1946 by agreement with the Egyptian Government, to conduct medical research on diseases endemic in this area.

‡ The original program was begun by Doctors J. H. Killough and G. B. Magill. Subsequent contributions have been made successively by Doctors S. I. Said, T. W. Burns, A. Badran, O. El-Alfi, W. C. E. Pfischner, E. M. Neptune, S. M. Fox, III, Z. Farid and K. G. Ishak.

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animals, whether they lived in a rural or urban environment. Furthermore, unpasteurized milk and cheese form a basic part of the Egyptian diet. The mode of transmission of brucellosis in Egypt will be difficult to establish until an

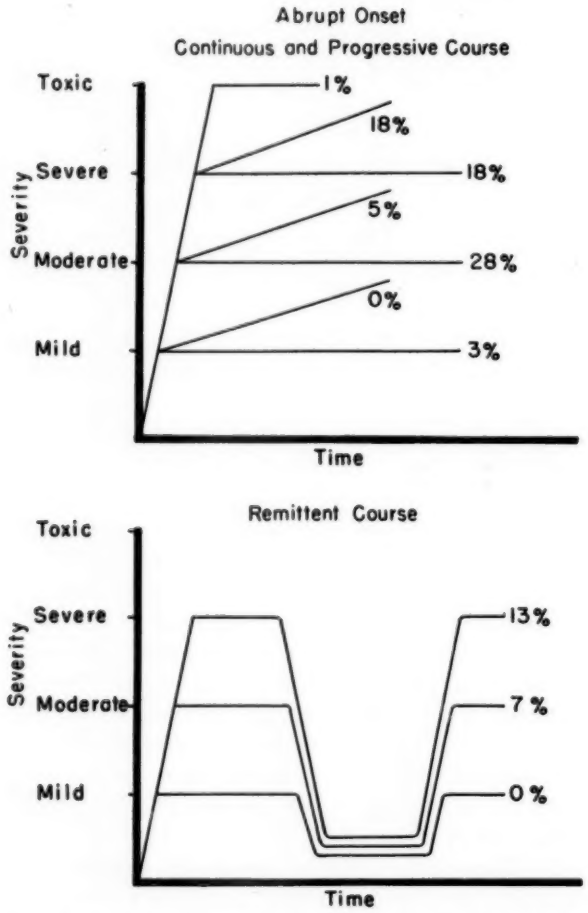

FIG. 1. Abrupt onset and subsequent course of brucellosis.

especially searching epidemiologic survey is undertaken.

Onset of complaints: According to Spink's classification [*10*] in which the duration of illness, irrespective of the severity of symptoms, is considered, these patients are classified into the various categories shown in Table II.

Figures 1 and 2 schematically portray the distribution of the different types of onset, severity and course of the disease in this study. These figures were used for the individual evaluation of each chart in which the total clinical picture was assayed. An abrupt onset was considered to be the sudden evolution of symptoms within a period of a few days. A gradual onset was one in which the patient slowly became aware of symptoms. In the latter group the patients were usually able to continue near normal activity for some time.

The progress of the disease can be followed in Figures 1 and 2. The diagrams of the remittent

TABLE I
AGE GROUPS AND DISTRIBUTION
(228 PATIENTS)

Age Group (yr.)	No. of Patients
10 or under	4 (2%)
11–20	43 (19%)
21–30	70 (31%)
31–40	61 (26%)
41–50	34 (15%)
51–60	12 (5%)
61–70	4 (2%)

TABLE II
DURATION OF ILLNESS PRIOR TO ADMISSION

Brucellosis	Duration (mo.)	No. Patients	Per cent
Acute	3 or less	201	88
Subacute	3–12	12	5
Chronic	12 or more	9	4
Not stated	.....	6	3

types give no indication of the marked variability that was present in this group but they do indicate the percentage of the total patients who had this remittent type course. The total number of patients represented in the diagrams is 222; in six patients the exact type could not be satisfactorily classified.

Complaints: The frequency of complaints and combination of complaints is shown in Figure 3 and Table III, respectively. A partial analysis of the combination of complaints is also given in Table III.

Weakness was present in the vast majority of patients. Malaise, or a feeling of general ill health, was recorded in 102 patients (45 per cent). When more severe symptoms predominated, malaise undoubtedly was present but was not recorded due to its relative insignificance.

The two most commonly associated complaints were fever and musculoskeletal pains, which were present in 151 patients (66 per cent). One hundred and two patients (45 per cent)

had no stated gastrointestinal complaints. The most frequent gastrointestinal complaint was anorexia, in fifty-one patients (22 per cent). Abdominal pain was complained of in twenty-one patients (9 per cent); it was of a vague and generalized character. Before therapy only

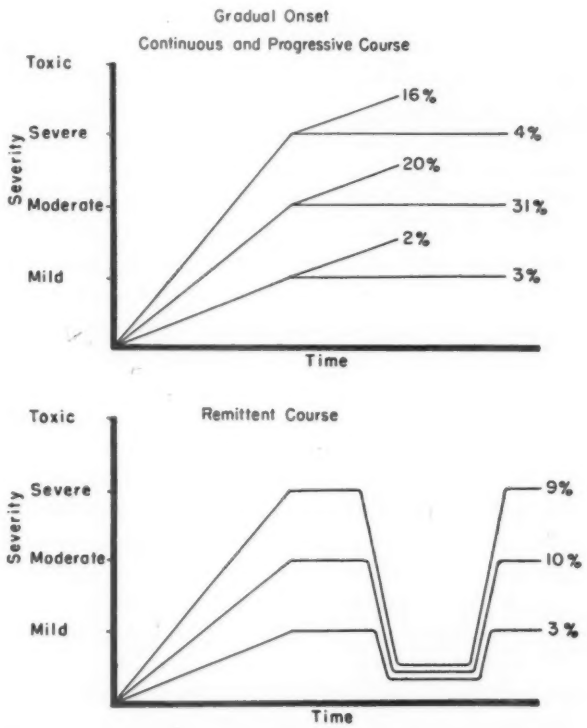

FIG. 2. Gradual onset and subsequent course of brucellosis.

twelve patients (6 per cent) complained of nausea, sixteen patients (7 per cent) complained of vomiting. Seven patients (3 per cent) complained only of diarrhea.

Thirty-seven patients (16 per cent) complained on admission of a dry unproductive cough. Twenty-four patients (11 per cent) had moderate sputum production without hemoptysis. Eight patients (4 per cent) complained of chest pain of a vague, generalized and ill defined type, which did not suggest a pleuritic etiology.

TABLE III
VARIOUS COMBINATIONS OF COMPLAINTS

Complaints	No. Patients	Per cent
Fever, sweats, musculoskeletal, headache	75	33
Fever, chills, musculoskeletal, headache	69	30
Fever, chills, sweats, musculoskeletal	59	26
Fever, chills, sweats, headache	59	26
Fever, chills, sweats, musculoskeletal, headache	42	18

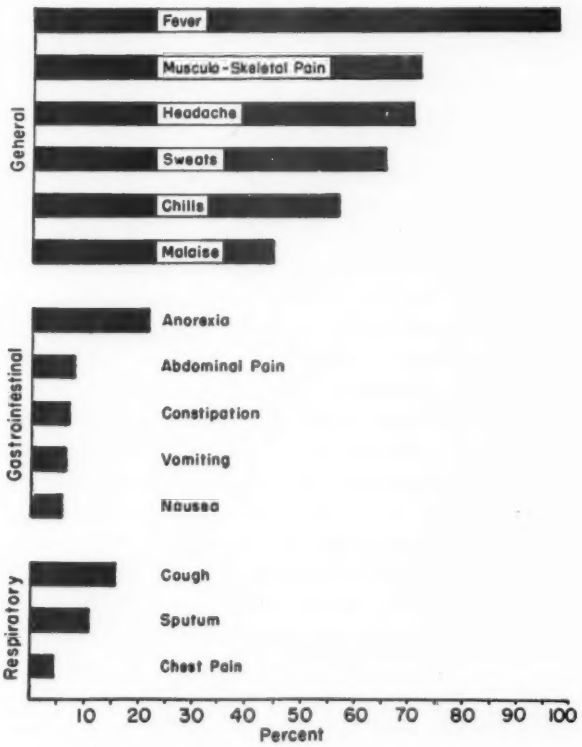

FIG. 3. Incidence of complaints on admission, 228 patients.

There were no stated genitourinary complaints on admission that could be attributed to brucellosis. A significant percentage, however, as will be mentioned later, were found to have urinary schistosomiasis with its attendant complaints.

Mental symptoms ranging from confusion to delirium were present in eight patients (4 per cent). These were present only when the patients were severely incapacitated by an illness which included many of the other previously listed general complaints.

Musculoskeletal pain, which included joint pains, bone and muscle pain, and backache was complained of by 164 patients (72 per cent). Backache was a specific complaint made by sixty-one patients (26 per cent) in this series but only nine patients had backache alone without associated joint pains.

Previous medications: Forty-nine patients (22 per cent) had received previous medication (sulfa-

diazine, twenty-one; chloramphenicol, twenty-four; penicillin, three; chloramphenicol and streptomycin, one) prior to admission to this Unit. Information concerning the exact duration and dosage of these varied medications was insufficient to warrant definitive analysis. This therapy undoubtedly altered or ameliorated the clinical picture in many of these forty-nine patients. Since all the patients had positive blood cultures for brucella, this medication was not considered of significant duration or intensity to invalidate the later therapeutic results.

Physical Examination and Findings. Fever was present in 98 per cent of our patients on admission. The fever prior to treatment was usually spiking in character, maximum fever occurring late in the afternoon and evening with a decline in the early morning hours.

On the basis of appearance as noted by the examining physician, sixty-eight patients (30 per cent) were classified as undernourished to emaciated. One hundred and sixty patients (70 per cent) were considered adequately nourished. The effect of brucella infection on the nutrition of these patients is difficult to evaluate because of multiple factors, bilharzia, intestinal parasitic infestations and other associated diseases. In view of the severe debility present in many patients in this series we would certainly expect a deleterious effect on the nutritional status. If the nutritional status of Egyptians of similar backgrounds without brucellosis is taken into considerations, however, a significant specific impairment of nutrition in brucellosis is not suggested by our data.

No effort was made to determine the incidence of vitamin deficiency by chemical studies but it is the authors' impression that vitamin deficiencies occurred roughly in the same proportions as reported by other authors working in Egypt [*11*]. Pellagra is the most common specific vitamin deficiency state. Beriberi is infrequently reported in Egypt. Vitamin C deficiency is not prevalent because of the availability of fruits and vegetables.

The appearance of the skin, hair and nails did not suggest any specific effects except those expected with the dehydration of hyperpyrexia or the avitaminosis already noted.

The majority of patients had small, discrete, non-tender, firm enlargement of lymph nodes localized largely in the cervical and axillary areas. Only three had more significant cervical node enlargement, and of these, two had grossly enlarged nodes involving the axillary, epitrochlear and inguinal areas.

Thirty-four patients (15 per cent) had minimal physical findings on chest examination (wheezes and rhonchi) but no radiographic evidence of parenchymal pulmonary involvement was noted in any instance. Routine chest films were taken upon admission.

Fourteen patients (6 per cent) had a grade 2 or 3 mitral systolic murmur. In all but one of these patients there was no change in the grade or type of the murmur, or in the clinical cardiopulmonary status to suggest a specific relationship to brucellosis. One patient on admission had a mitral systolic murmur. On discharge one year later, after repeated febrile episodes treated by various antibiotics, mitral and aortic systolic and diastolic murmurs were heard. During the hospitalization of this patient thirty-three venous blood cultures were positive for brucella. No other organism was isolated. The electrocardiogram showed left bundle branch block. The patient was considered to have rheumatic heart disease and brucellosis. The possibility of a superimposed brucella endocarditis was considered.

On admission, hepatomegaly was noted in 141 patients (62 per cent) and splenomegaly in 159 (70 per cent); one hundred and eighteen patients (52 per cent) had both hepatomegaly and splenomegaly. Of the 141 patients with hepatomegaly on admission (62 per cent), the average extension of the liver below the right costal margin in the mid-clavicular line was 3.7 cm. Upon discharge, hepatomegaly persisted in ninety-seven (43 per cent) of those patients in whom it was noted on admission. There was a decrease in size of the liver of over 1 cm. in ninety-five patients (67 per cent), an apparent increase of over 1 cm. in seventeen patients (12 per cent), and no apparent significant change in twenty-three patients (16 per cent). The data on the remainder were not adequate for analysis.

Splenomegaly, when noted on admission, decreased over 1 cm. in extent in 119 patients (75 per cent). An apparent increase in size of over 1 cm. in extent was noted in nine patients (6 per cent), and no apparently significant change in nineteen patients (13 per cent).

Because of the high incidence of parasitic and protozoal intestinal infestations in 194 (85 per cent) of these patients, and schistosomiasis in seventy-eight patients (39 per cent), the role of brucellosis in the etiology of the hepato-

splenomegalies could not be clearly determined. Only forty-four patients (23 per cent) were treated here for these associated diseases, the majority being referred to government treatment centers after discharge.

One hundred and sixty-four (72 per cent) of 228 patients complained of one or another form of musculoskeletal pain on admission. The knees, ankles, shoulders, wrists, elbows and hips were frequently involved, in various combinations. Three patients were unable to walk because of back pain, which was usually most pronounced in the lumbosacral area. In only three patients was there objective evidence of joint involvement (in three, knees; in one, ankle) with redness, swelling, heat and tenderness on palpation and movement. These patients showed no radiographic evidence of bone or joint change. Others had pain on local pressure but did not appear to have a true arthralgia. In most patients joint and bone manifestations subsided coincident with treatment, and 220 patients were asymptomatic on discharge. In the remaining eight patients the symptoms on discharge were referable to the joint pains complained of on admission but to a much lesser extent.

The average pretreatment observation period was one week. The average maximum fever prior to treatment was as follows: Three (1 per cent) in the 98.6° to 99°F. range, 122 (54 per cent) in the 99.1° to 102°F. range, eighty-nine (39 per cent) in the 102.1° to 104°F. range, and fourteen (6 per cent) in the temperature range over 104°F. The representative evening temperature during the active phase of the pre-treatment observation period was as follows: Ninety-nine patients (44 per cent) between 100° and 102°F., eighty-six (39 per cent) between 102° and 104°F., thirty-eight (17 per cent) between 98° and 100°F.

LABORATORY DATA

Hematologic Data. The differential blood count on admission was reviewed in 218 patient records, and an initial lymphocytosis was present. The mean value for the lymphocytes was 40 per cent with a standard deviation of ±11; when, however, a control group of thirty-six asymptomatic and healthy Egyptians was studied, the mean value for the lymphocytes was 42 per cent. The mean lymphocyte value on discharge was 46 per cent in 208 of these same patients in whom a differential white blood cell count was done. The admission absolute lymphocyte values for the patients was 2,680 with a standard deviation of 1,400 and a standard error of 130. The control group had a mean value of 2,820 with a standard deviation of 1,000 and a standard error of 170. There is no significant difference between the two groups ($P > 0.5$).

TABLE IV
WHITE BLOOD CELL COUNT

Cell Count	Admission		Discharge		Controls	
	No. of Patients	Per cent	No. of Patients	Per cent	No. of Patients	Per cent
Leukopenia (4,000 or less)	38	17	14	7	4	11
Normal (4,000–10,000)	164	74	166	80	28	77
Leukocytosis (over 10,000)	21	9	28	13	4	11

In forty-six brucella patients without demonstrated parasitic disease the blood eosinophils determined by differential white blood cell count had a mean value of 0.5 per cent (S.E. ± 0.03). When compared to our control group of Egyptians who had a mean eosinophile value of 2.8 per cent (S.E. ± 0.3) this represents a significantly lower value for the patients with brucellosis ($P < 0.01$). The mean eosinophil value on discharge for this group of patients was 4.4 per cent (S.E. ± 0.07). The possible significance of this depression of eosinophils in untreated brucellosis, and the later rise following treatment, has not been determined. Further study is certainly indicated to ascertain whether or not the differences between the brucella and control group might be related to such factors as bed rest versus normal activity, and not specifically related to brucellosis itself.

Table IV lists the total white blood cell counts for 223 patients on admission and 208 patients on discharge

On admission, 202 brucella patients had a mean hemoglobin value of 12 gm.

Brucella Agglutination Test. The brucella agglutination titre was determined in all patients on or prior to admission. A titre of 1/160 or greater was an admission criterion, and thus all our patients had titres of 1/160 or greater. The results of the admission and discharge brucella agglutination titres are shown in Figure 4. These two curves show a definite fall in the agglutination titre on discharge as compared to admission. The apparent double peak in this

diagram is a result of the last figure being an aggregate of those with titres of 1:10,240 or greater. These data are not to be construed as truly representative in the epidemiologic sense since, as already mentioned, only those patients

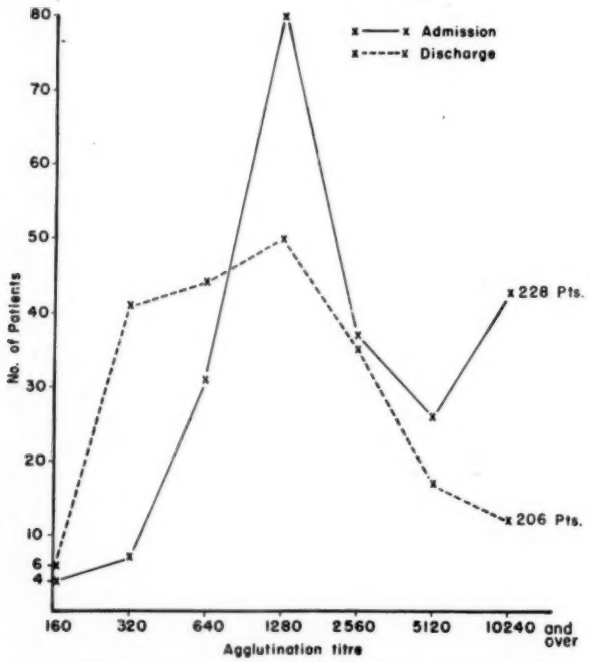

FIG. 4. Comparison between brucella agglutination titres on admission and on discharge.

were selected who had strongly suggestive histories and laboratory findings and therefore many persons who had early or mild brucellosis were probably not included. Of the total of 228 patients, 206 had a brucella agglutination determination on discharge.

The majority of relapses following initial treatment occurred so promptly that there was insufficient time to observe serologic trends of the brucella agglutination titre.

Figure 5 shows changes in brucella agglutination titre following completion of apparently successful treatment. These data were collected from the total group of forty-one patients who had an admission brucella agglutination titre of 1:10,240 or greater. The shaded areas represent the standard error from the mean value which is plotted with open circles. It is seen that the fall of the agglutination titre to nearly normal levels occurred approximately twelve months after the end of successful therapy. Patients who had lower titres on admission had a parallel fall in titres similar to this 1:10,240 group.

Brucella Blood Cultures. All 228 patients had positive cultures for Brucella melitensis. Blood cultures for the detection of brucella were made according to the two-phase technic described by Castaneda [*12*]. In this study, trypti-

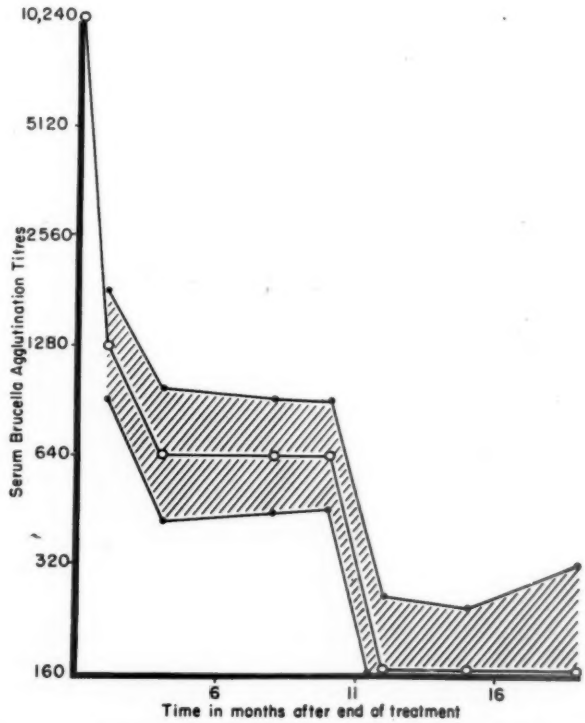

FIG. 5. Changes in brucella agglutination titre following completion of apparently successful treatment.

case soy agar (BBL) was used instead of the liver infusion agar employed by Castaneda.

Colonies which developed on the agar layer were identified as brucella by taxonomic characteristics and by their inability to ferment carbohydrates. Species determination was accomplished by means of the dye tolerance reactions described by Huddleson [*13*].

On admission, the usual routine was to take one venous blood culture daily for the first four days, if the temperature was normal. On the occurrence of each upward rise in temperature another blood culture was obtained. After treatment was begun cultures were taken on an average of twice weekly, and also approximately twice weekly during the post-treatment observation period until discharge. This was found necessary because of intervals during which negative cultures were obtained yet typical symptoms then present were only later accompanied by the finding of brucella organisms. It was also found

that positive cultures were obtained in the absence of clinical complaints in some instances. The average number of venous blood cultures during hospitalization was over twenty-six per patient. The distribution of positive, negative and contaminated cultures per patient during the pretreatment, treatment and post-treatment observation periods is illustrated in Figure 6. Since a variety of therapeutic agents was used during the six-year period with varying success, the results after therapy was started indicate only the laboratory problems involved in a brucellosis study and do not represent the expected response to optimum treatment.

TABLE V
ASSOCIATED DISEASES

Associated Diseases	No. Patients	Percentage
Schistosomiasis	78	34
Ankylostomiasis	70	31
Amebiasis	55	24
Ascariasis	34	15
Giardia lamblia	34	15
E. nana	27	12
Trichostrongyloides	13	6

Urine Cultures. Urine cultures were obtained from 172 patients (76 per cent), the total number of cultures being 3,149. They were discontinued in the latter part of the study because of the large percentage of non-brucella organisms which grew out previous to the time the brucella organisms were expected. The inconvenience and possible hazard to the patients of repeated urethral catheterizations was also a consideration. In patients with a positive urine culture, a positive blood culture was invariably obtained. In no instance were urine cultures positive for brucella when blood cultures were negative. On the other hand, urine cultures were negative in 101 patients (59 per cent) from whom one or more blood cultures were positive for brucella. In two instances epididymo-orchitis developed during hospitalization in patients who were catheterized. There were no such episodes in the larger number not catheterized.

Marrow Cultures. Marrow cultures were taken from thirty patients included in this series. The findings were reported by Hamilton [*5*] in a previous publication. He concluded that venous blood culture is a better method of diagnosis than bone marrow aspiration and culture.

Concomitant Diseases. In the Egyptian patient, whenever the question of the evaluation of disease arises the investigator finds himself confronted with a number of other parasitic and protozoan infestations which complicate all aspects of the disease under primary study. This difficulty obtained in the present study. Of our 228 brucella patients, 194 (85 per cent) were found to have one, two or more diseases as shown in Table v.

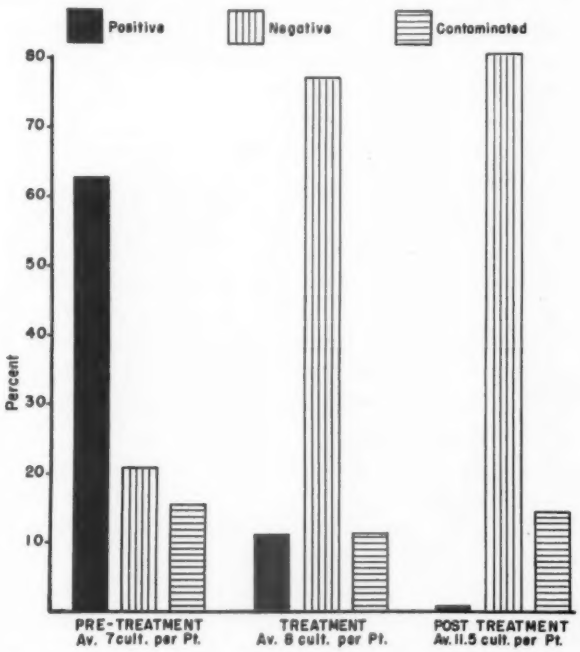

FIG. 6. Results of venous blood cultures during pretreatment, treatment and post-treatment periods.

RESPONSE TO THERAPY

Previously published reports from this Unit on the therapy of brucellosis with single and combined antibiotic therapy [*1,2,4,6,7,8*] will not be extensively reviewed here. Suffice it to say that with single antibiotic therapy, such as chlortetracycline, oxytetracycline and chloramphenicol, the relapse rate approached 80 per cent. Similarly, our experience with erythromycin alone in thirty-four patients showed a therapeutic failure in twenty-five (73 per cent) [*7*]. With combined antibiotic therapy (oxytetracycline and streptomycin) the incidence of relapses was reduced to 14 per cent [*2*]. Our more recent experience at this Unit with erythromycin and streptomycin-dihydrostreptomycin in forty-four patients has resulted in a therapeutic failure in 9 per cent [*7*]. Our definition of therapeutic failure is: (1) failure to respond clinically; (2) clinical relapse

within sixty days after treatment, or (3) bacteriologic relapse within sixty days after treatment. The average follow-up in this group, after discharge, has been six months. A series of sixteen patients was treated with tetracycline alone and two therapeutic failures were noted, with an average follow-up of three months after discharge. A separate report dealing with these last two mentioned treatment groups (erythromycin and streptomycin and tetracycline) is in preparation [*14*].

To date the role of natural and acquired immunity in brucellosis in man is only vaguely understood, although some light has been shed on this aspect of the disease by various workers [*15,25,57,58*]. We have had no experience with antigen therapy in brucellosis since its proponents advocate it mainly in the chronic illness which we have not encountered in our study.

The average weight gain per patient during hospitalization was 17 pounds.

The average observation period in the hospital following treatment was twenty-seven days. The average duration of follow-up of the 228 patients after discharge was eleven months.

Of the 228 patients in this study on all forms of antibiotic therapy, 220 were asymptomatic on discharge. In the remaining eight patients the symptoms on discharge were referable to the musculoskeletal complaints present on admission but to a much lesser degree.

DIFFERENTIAL DIAGNOSIS

We agree with Harris [*15*] who states: "Brucellosis must be considered in the differential diagnosis of any obscure illness, acute or chronic, febrile or afebrile."

In the light of our experience in Egypt, certain diseases assume a more prominent place in our differential diagnosis of brucellosis and are here listed in the approximate order of their relative frequency or importance in Egypt.

Paratyphoid and Typhoid Fever. These two conditions, with their variable onset, headache, malaise, leukopenia and splenomegaly, may be impossible to differentiate from brucellosis. The steplike rise in temperature, the slow pulse in relation to the fever, the appearance of rose spots, the abdominal manifestations, rising specific agglutination titre and isolation of the organism from the stools, urine and/or blood may be the differentiating points. We have had more trouble in differentiating the less acutely toxic paratyphoid than the typhoid cases.

Pulmonary Tuberculosis. Pulmonary tuberculosis may be confused with the chronic or insidious form of brucellosis. The diagnosis must depend on identification of the tubercle bacilli by smear and/or culture and radiographic evidence of lesions. Brucella complications such as spondylitis and osteomyelitis may resemble tuberculosis of the tissues or bones. Brucellosis and pulmonary tuberculosis may occur together and this should be kept in mind. We have not seen such cases.

Rheumatic Fever. In its atypical forms this disease may be very difficult to differentiate from brucellosis. Careful observation for the major manifestations of rheumatic fever (carditis, arthralgia, chorea and subcutaneous nodules), a past history of rheumatic fever or the presence of rheumatic heart disease will help to clarify the diagnosis. A leukocytosis and positive antistreptolysin O, antistreptokinase and the antihyaluronidase reaction, and the presence of more objectively demonstrable arthritis and positive electrocardiographic changes also favor the diagnosis of rheumatic fever. A recent article by Peery [*16*] emphasizes the similarities between rheumatic fever and brucellosis.

Rheumatoid Arthritis and Hypertrophic Arthritis. One of the most useful points in the differentiation of rheumatoid arthritis from brucellosis is the usual presence of objective joint involvement with deformity, and later, the radiographic changes found in rheumatoid arthritis. In approximately 70 per cent of the cases of rheumatoid arthritis the serum of the patient agglutinates group A hemolytic streptococci [*17*].

The degenerative arthritides and gonococcal arthritis must also occasionally be differentiated from brucellosis.

Malaria. Brucella infection with a sudden rise of temperature accompanied by chills and profuse sweating may closely simulate an attack of malaria. The diagnosis of malaria is established by demonstrating the malaria parasites in the blood smear. The endemicity of malaria in Egypt, with the typical periodicity of attacks may be further differentiating factors. We have seen only two brucella patients of over a hundred in our personal experience who had a shaking chill of the more severe malarial type.

Influenza. With its sudden onset of fever, marked prostration and severe aching pains in the back and extremities influenza may simulate brucellosis but it is self-limited and, when uncomplicated, of relatively short duration in con-

trast to the persistence of these symptoms in brucellosis. The absence of nasopharyngeal symptoms would tend to favor the diagnosis of brucellosis.

Subacute Bacterial Endocarditis. Therapeutic response to penicillin may be the only possible differentiation between subacute bacterial endocarditis and the complicating endocarditis due to brucella. If blood cultures are negative for streptococci or brucella organisms the secondary aids of specific agglutinations and the finding of foci of entrance or extracardiac persistence of the organism are needed.

Musculoskeletal pain does not occur frequently in subacute bacterial endocarditis.

Hodgkin's Disease and Febrile Malignancies. The lymphadenopathy, malaise, weight loss and hepatosplenomegaly in these disorders may cause confusion with brucellosis. Negative serologic and cultural studies and positive biopsy should in the majority of cases differentiate these diseases. Some authors, notably Poston [*18*], Poston and Parsons [*19*], Wise and Poston [*20*], Harris [*15*] and Forbus [*21*] have described the chance concurrence of brucellosis and Hodgkin's disease.

Lupus erythematosus and other "collagen" diseases, periodic fever [*22*], infectious mononucleosis, infectious hepatitis, Q fever, meningitis, pyelonephritis, the mycoses, hyperthyroidism, and psychoneurosis may all on occasion have to be differentiated from brucellosis. In tropical and subtropical areas typhus and relapsing fever, leptospirosis, filariasis, schistosomiasis, amebiasis, trichinosis, kala-azar and trypanosomiasis may simulate brucellosis and differentiation must be established by history, physical examination and appropriate laboratory tests.

In summary, then, in Egypt the diseases most easily confused with brucellosis are in the paratyphoid-typhoid, tuberculosis, influenza, malaria and rheumatic fever groups. In other areas, notably the United States, the parathyroid-typhoid and tuberculosis group would be less important and probably displaced by infectious hepatitis, infectious mononucleosis and possibly influenza.

COMMENTS

Brucellosis is an unusual disease. It is not similar to the acute febrile diseases such as the exanthemata due to bacterial infection; in these diseases a climax is reached and the patient succumbs or recovers with the aid of a specific immune response. In the bacteremic phase, however, the clinical picture of brucellosis may closely resemble any of the acute septicemic diseases. In the general biological sense and in the intermittent pattern of relapses, the disease resembles malaria. Both have an active phase usually associated with symptoms and a tissue phase which is more difficult to eradicate. In some respects brucellosis is similar to tuberculosis. It is a chronic disease with an ill-defined immune response that can cause granulomatous lesions and may involve the lymph nodes, bones and lungs. It is rarely, however, as destructive as tuberculosis.

Since brucellosis is often ill-defined with varied manifestations, and since it is widespread in occurrence, we have attempted in this report to give a definitive picture of the disease as it occurs in Egypt. In this discussion our comments are largely limited to those points which are at variance with or add significance to other reports.

Eighty-eight per cent of the patients in this study had an illness of three months or less and this is in agreement with Hardy et al. [*23*] who reported 87 per cent of 230 patients to have an acute illness of less than two months. Harris [*24*], however, stated that only 10 per cent of 421 patients were ill for three months or less and Spink [*10*] found that only 16 per cent of sixty-five patients were ill for three months or less. In reporting several smaller series Spink [*25,26*] stated that 43 per cent and 53 per cent were ill for three months or less. There are several possibilities for these apparent discrepancies. In some of the studies mentioned patients were included who did not have positive blood cultures and presumably did not have active bacteremia. Our patients, on the other hand, were selected usually from nearby hospital populations and we have no information on how many Egyptians may have a mild or chronic form of the disease and have not requested hospitalization. Furthermore most of the brucellosis reported from the United States is caused by Br. abortus whereas the disease in Egypt is almost invariably caused by Br. melitensis. Since the latter has been described as more invasive [*10*], this may be the reason for the more acute onset and severe course.

Fever was present on admission in 98 per cent of our patients. In the majority of patients it was spiking in character during the pretreatment observation period. The maximum fever of any

one day usually occurred in the late afternoon and evening, with a temporary return toward normal levels in the early morning hours. This corresponds to Spink's description [*27*] in which he stated that the most common fever pattern is a diurnal intermittent variation, with normal values at the beginning of the day and elevations in the afternoon or evening. Spink [*27*] also states that the undulating type of fever is more frequently seen in infections due to Br. melitensis. Hall [*28*], Simpson [*29*] and Howe [*30*] have similarly commented upon these same characteristics of temperature change.

The symptomatology reported in this study is in many ways similar to that reported elsewhere. Weakness and fever were present in nearly all patients. Joint pain, however, was present in 68 per cent of our patients whereas Spink [*31*] and Hall [*28*] reported only 44 per cent and 31 per cent, respectively. Cough and anorexia were much less common than reported by both of these authors.

In considering the physical findings in this study, lymphadenopathy was noted in the majority of our patients and is also reported by others [*3,27,28,31–33*]. The nodes were usually small, discrete and non-tender, the cervical and axillary areas being most frequently involved. Hepatomegaly (70 per cent) and splenomegaly (62 per cent) occurred much more frequently than the 45 per cent and 26 per cent reported by Spink [*31*] and 43 per cent and 34 per cent reported by Hall [*28*]. Since hepatosplenomegaly is frequently found in Egyptians suffering from other diseases, particularly bilharziasis, the data were examined in another manner; only those patients whose spleen and liver definitely decreased in size following therapy were tabulated, the hypothesis being that the remainder had hepatosplenomegaly from other causes. Forty per cent had splenomegaly and 20 per cent had hepatomegaly which decreased following brucella therapy. These figures are much closer to those reported above.

Although the serologic agglutination test is of value for screening and detection it does not have a specific diagnostic value for detecting active disease. We have noticed, however, that a drop in the agglutination titre does occur over a period of months in the majority of patients. In the few patients who relapsed several months after therapy there was a beginning rise in agglutination before blood cultures became positive. This suggests that it is worthwhile to follow the agglutination titre for two or more years after therapy.

A positive blood culture is the main criterion for diagnosis of the original disease or relapse. Since we have not seen the chronic brucellosis described by Spink and others, there has been no necessity to rely on presumptive diagnostic procedures. Prior to treatment, seven venous blood cultures, on the average, were drawn on each patient. Of these cultures approximately 65 per cent were positive for brucella, 20 per cent were negative and 15 per cent contaminated. Therefore in our experience it would seem that at least seven or eight blood cultures should be drawn prior to institution of therapy to be reasonably sure that at least one positive culture will be obtained. Urine cultures appear to be of little value in the diagnosis of brucellosis as compared to blood cultures.

Two other diagnostic tests have been used by other workers but we have had no experience with either of them. The intradermal test is generally interpreted, when positive, as an indication that the person has at some time in the past developed a hypersensitivity to brucella organisms. A positive skin test does not necessarily give any indication of active infection. Since there are wide variations resulting from the use of different antigens and since it has been suggested [*27*] that administration of the intradermal antigen may cause an elevation of serum agglutinins, the value of the intradermal test is questionable at this time [*56*].

The opsonocytophagic test, which is a measure of the ability of polymorphonuclear neutrophils to ingest viable brucella organisms, has been discarded by Spink [*10*] because it is technically difficult and is undependable for diagnostic purposes. WHO [*56*] has also reported it as unsuitable for routine diagnostic use.

The majority of our patients had a normal white count. Only one patient in ten had an elevated white count. Seventeen per cent of the patients had a leukopenia. This is a smaller number with leukopenia than would be expected in comparison with the data of others [*10,28*]. Although lymphocytosis is reported as common by Spink [*10,27*], Hall [*28*] and others, there is no significant difference between the percentage of lymphocytes in our patients ill with brucellosis and a control group of healthy Egyptians. However the values for both groups (between 40 per cent and 45 per cent) are higher than the usually accepted normal. Since there was no

significant alteration between the admission and discharge lymphocytic counts, it is assumed that brucellosis did not affect the lymphocyte count in this series.

The authors regret the lack of pathologic data on brucellosis in this report. None of the 228 patients died and the authors did not have the opportunity to perform or attend autopsies on patients with this disease. Lymph node or liver biopsies were not attempted on any of the patients. The bone marrow findings in acute brucellosis were reported on by Hamilton [*5*] from this Unit. The pathology of the disease, however, has previously been described by numerous authors [*15,23,32,34,35*].

Of special note in this series is the low incidence of complications due to brucellosis, such as osteomyelitis, endocarditis, hepatitis, encephalitis, meningitis or pneumonitis. Brucella infection of bone and joints as reported by various authors [*15,32,36–40*] has not been observed in our patients. Psychologic and neurologic complications also have not been observed by us but are reported by Apter et al. [*41*], Spink and Hall [*42*], Ley and Stauder [*43*], Nelson-Jones [*44*], Harris [*15*] and Nichols [*45*]. Only one of our patients was suspected of having a superimposed brucella endocarditis. This is an infrequent complication in patients with brucellosis but has been reported by a number of authors [*46–48*]. A recent article by Peery [*16*] gives an excellent review of the subject of brucellosis and chronic cardiac valvular disease. Apart from early transient bronchitis in some of our patients no pulmonary complications have been noted by us. A review of the literature on pulmonary brucellosis by Harvey [*33*] suggests that it is a manifestation frequently encountered and unrecognized. The characteristic clinical course in pulmonary brucellosis is marked by perihilar lymphadenopathy, bronchitis or pneumonitis of prolonged duration and usually by spontaneous subsidence with resorption or fibrosis. Only one of our patients in this series had hepatitis but the etiologic relationship to his brucellosis was not proved. Hepatitis has been noted by others [*15,32,49,50*]. Spink [*27*] states that brucella localize in the liver quite frequently. A constant finding observed by his group following biopsy of the liver in patients with infections due to Br. abortus has been an inflammatory reaction with granulomas in the parenchyma. While most of these hepatic lesions are benign and provoke no demonstrable residue, evidence is accumulating that brucellosis may be an important contributing factor in the genesis of some cases of cirrhosis of the liver. Brucella hepatitis leading to cirrhosis of the liver has been reported by McCullough and Eisele [*51*].

The vital statistics on brucellosis in Egypt [*52*] covering the years 1943 to 1954, inclusive, record only 585 cases with twenty-seven deaths. Current thinking among most observers in Egypt is that the disease is much more prevalent than is indicated by the data cited, and that many cases understandably remain unrecognized or are confused with other diseases because of the limitations of diagnostic facilities. No epidemiologic surveys had been conducted in this country until the recent survey of the WHO in conjunction with this Unit [*53*]. Riding [*54*] and later Gohar [*55*] have made surveys on selected groups of people but the selection unfortunately does not permit general epidemiologic application. The incidence of the disease in animals is unknown.

It is established that the principal routes of transmission of the disease from animals to man are ingestion, contact, inhalation and inoculation [*56*]. Although it has been emphasized previously in this paper that the mode of transmission of brucellosis from animal to man in Egypt will remain undetermined until a specially designed epidemiologic survey is undertaken, it is believed by the authors that the daily intimate contact between man and animals such as occurs in Egypt may be the most important factor in the spread of the disease. The hot, dry, dusty climate would facilitate airborne dissemination of the disease from the excreta of infected animals. Flies probably also play a part as vectors of the disease. Goats, sheep, gamoose (water buffalo), cows, donkeys and camels probably comprise the majority of animals most concerned in the spread of the disease in Egypt. The Egyptian farmer associates intimately with these animals during his daily work and home life. The absence of any widespread pasteurization of milk should be considered the second most important factor in the spread of the disease. Combat of the disease will be possible only when infected animals are destroyed, and pasteurization of milk made compulsory.

After institution of specific therapy the temperature usually returns to normal levels within five days. Following this, the general condition of the patient improves, with return of appetite,

disappearance of malaise and headache, and diminution of musculoskeletal pain. Residual joint pains occasionally persist into the post-treatment observation period. Regardless of the form of therapy used, the majority of patients are asymptomatic on discharge and are able to resume their former work.

The therapeutic approach to the problem of brucellosis in Egypt does not resolve itself into specific treatment alone but must take into consideration the associated diseases and nutritional disorders. Nearly all the patients showed a definite weight gain from admission to discharge. This was probably the outcome of a combination of factors including the response to specific therapy, physical rest from the strenuous activity in which most of these were engaged prior to admission, and the more nutritious and balanced hospital diet.

In the background of the total problem of the therapy of brucellosis is the fact that the disease has two distinct phases, the bacteremic phase and the intracellular phase. Therefore, the effectiveness of any form of therapy depends both on the eradication of the circulating organisms and on the ability of the drug to reach the intracellular organisms in effective concentration [*8*].

It is quite obvious from the literature that effective therapy of brucellosis requires the use of at least two antibiotics, given concomitantly. A detailed listing of the efficacy of the various therapeutic agents has been reported by the WHO [*56*].

Today, optimum therapy of the acute disease seems to require the use of streptomycin or dihydrostreptomycin in combination with one of the broad-spectrum antibiotics. The best results in our experience have been with erythromycin and streptomycin [*7,14*]. It must be kept in mind that adequate dosage and sufficiently prolonged administration are required for successful treatment [*14*]. Detailed reports concerning the therapy of brucellosis have been previously published by workers from this Unit [*1,2,4,6–8*].

SUMMARY AND CONCLUSIONS

1. This presentation is a review of 228 cases with bacteriologically proved brucellosis studied at the United States Naval Medical Research Unit, Cairo, Egypt from 1952 to 1956.

2. The patients were selected on the basis of a suggestive history and a brucella agglutination titre of 1/160 or higher.

3. The commonest age incidence (57 per cent) was between twenty-one and forty years. Most of the patients in this study were males (due to lack of facilities for accommodating females).

4. The epidemiologic background of the disease in this series has not been studied. It is believed, however, that the source of infection in most cases was intimate contact with infected animals and the ingestion of unpasteurized milk or milk products.

5. The mode of onset and subsequent course of the disease are schematically represented in Figures 1 and 2

6. Fever was the most common complaint, followed by musculoskeletal pain (including joint, muscle and bone pain, and backache), sweats, chills and malaise in that order of frequency. Gastrointestinal complaints were minimal, anorexia being the most frequent. Only a small percentage of patients complained of cough, excessive production of sputum or of chest pain.

7. Previous medication had been administered to forty-nine patients (22 per cent) but was not considered of significant duration or intensity to invalidate later therapeutic results.

8. Apart from the fever, the physical findings on admission were lymphadenopathy in the majority of patients, hepatomegaly in 62 per cent and splenomegaly in 70 per cent of patients. Because of the high incidence of schistosomiasis and other parasitic and protozoal infestations in these brucella patients the role of brucellosis in the etiology of the hepatosplenomegalies remains undetermined.

Objective joint manifestations were noted in only three patients and no radiographic changes were demonstrated.

9. Nutritional disorders and avitaminoses were found in the same proportions as reported by other workers from this country in the population at large.

10. The maximum fever in the pretreatment observation period ranged from 99.1° to 102°F. in 54 per cent of the patients. In 39 per cent the fever ranged between 102.1° and 104°F. The pretreatment representative evening temperature range during the active phase of the disease in 44 per cent of our patients was between 100° and 102°F. In 39 per cent of the patients the fever ranged between 102° and 104°F. The fever was usually spiking in character, maximum fever

occurring late in the afternoon and evening and decreasing in the early morning hours.

11. In this series no significant difference was observed in the lymphocyte count on admission between the brucella patients and a control group of healthy Egyptians. The eosinophil count was depressed on admission and showed a later rise following treatment in those patients suffering from brucellosis unassociated with other diseases. The authors have no explanation for this finding.

12. All patients had an admission agglutination titre of 1/160 or greater. A comparison between admission and discharge agglutinations, as well as the follow-up agglutination titres, is illustrated in Figures 4 and 5, respectively. In Figure 4 a definite fall in the agglutination titre is shown to occur between admission and discharge. In Figure 5 it is seen that there is a fall to nearly normal levels in the agglutination titre in the group with a titre of 1:10,240 by the twelfth month following successful therapy.

13. On the average, seven blood cultures per patient were necessary in the pretreatment observation period in order to ensure at least one positive culture. During and following successful therapy blood cultures were also drawn at intervals according to a fixed schedule. Follow-up agglutination titres and cultures were also obtained.

14. Urine cultures were found to be inferior to blood cultures in diagnosis and were discontinued in the latter part of the study.

15. Marrow cultures were taken from thirty patients included in this study. Venous blood cultures proved better from a diagnostic point of view.

16. Concomitant parasitic and protozoal infestations were present in 85 per cent of the brucella patients in this study. The most important of these were schistosomiasis, then amebiasis, ankylostomiasis and ascariasis.

17. Of special note in this series is the low incidence of complications associated with the original disease. One patient had hepatitis during the active phase of his brucella infection but no etiologic relationship to his brucellosis was proved. Another of our patients was suspected of having a superimposed brucella endocarditis.

18. The diseases most easily confused with brucellosis in Egypt are paratyphoid fever, typhoid fever, tuberculosis, influenza, rheumatic fever and malaria.

19. Today, optimum therapy seems to require the use of streptomycin or dihydrostreptomycin in combination with one of the broad-spectrum antibiotics. It must be kept in mind that adequate dosage and sufficiently prolonged administration are required for successful treatment.

20. The average observation period in the hospital following treatment was twenty-seven days, and the average duration of follow-up was eleven months. Nearly all patients were asymptomatic on discharge.

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Clinical Evaluation of Enzymatic Therapy in Diseases of the Chest*

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THE therapeutic use of proteolytic enzymes has become widespread during the last few years. There is now a great deal of information about the indications, therapeutic effects and complications in the use of several of these enzymes. The purpose of this review is to attempt to survey the position that has now been reached in enzyme therapy.

The introduction of new substances into our therapeutic armamentarium results in changes, often very great, in our approach to therapy. As new substances are developed, clinical trials in many scattered centers are reported as rapidly as possible in order to establish the usefulness of a proposed therapeutic agent. The need for speed in report is obvious. The sooner a valuable new therapeutic agent can be brought into general use the better. However, the very speed with which such reports are produced commonly does not allow adequate assessment of long-term therapeutic usefulness and possible disadvantages that appear more gradually with more prolonged study. In a small series of cases immediate toxic manifestations may be hidden from the observer simply by the low statistical probability of their occurrence. Late toxic manifestations cannot, of course, be noted at all. The true therapeutic usefulness of a new agent cannot be accurately evaluated except with wide experience over a prolonged period of time.

This is not to decry the many valuable and excellent reports both from the laboratory and the bedside that appear in the medical literature on new therapeutic agents; it is to emphasize that the widespread use of powerful drugs tends to precede the complete evaluation necessary to understand both the therapeutic usefulness and the incidence and nature of toxic effects. Our eagerness to improve our methods of treatment is a sufficient reason why this must be so.

General Principles of Enzyme Therapy. Enormous numbers of enzymes with varying functions are present in the body. Some of these substances are broad-spectrum enzymes capable of catalysing changes in many types of dissimilar substrates. Others are very narrow in action acting only upon a specific substrate, causing a single chemical change. Moreover, enzymes in various places in the body may be totally different in type, and when placed in a new site may cause considerable disruption of the local body economy. Proteolytic enzymes are present in the digestive tract and in all cells. However, the proteolytic enzymes of the digestive tract are different from those present in cells. Cellular proteolytic enzymes commonly work either by breaking down a substrate into simple molecular aggregates or they may be involved in biosynthesis, for example, the synthesis of proteins from amino acids. Although trypsin can form polypeptides from amino acids, its essential function is to break down proteins into soluble dipeptide compounds. The intracellular proteolytic enzymes manifest their proteolytic activity mostly after cell death when autolysis of tissue takes place.

When abnormal coagula occur in the human body there is a considerable risk of infection and of local loss of function. This is particularly true in the pleural space where blood clot, particularly postoperatively, may give rise to empyema. Even in the absence of infection, organization of fibrin may give rise to pleural adhesion, fibrosis and loss of pulmonary function. The introduction of proteolytic enzymes into a pleural space containing a large blood clot would, in theory, prevent this chain of events. We must use enzymes not normally present in the pleural cavity in order to accomplish this however. It was in this context that

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Tillett and Sherry [*1*] reported the first considerable clinical trial with a proteolytic enzyme in diseases of the chest.

The use of intrapleural enzymes was extended to include cases of empyema with massive fibrin deposition on the pleural wall. Aerosols were applied in conditions in which sticky, tenacious mucus in the bronchial tree was embarrassing respiration and causing local pulmonary atelectasis and infection.

Three groups of enzymes have been employed on a considerable scale in clinical study of these conditions: streptococcal fibrinolysis with desoxyribonuclease (dornase) referred to as SkSd, trypsin prepared from animal pancreas, and desoxyribonuclease prepared from animal pancreas. There have been a few reports on the use of other enzymes, such as papain, lysozyme and others, but these have not been studied on the same scale as the preceding group.

Enzymes under Consideration in the Therapy of Diseases of the Chest. Streptokinase (Sk): This is derived from Lancefield Group C beta hemolytic streptococci. It is an exotoxin with fibrinolytic properties. Its function normally is in streptococcal dissemination. It has relatively no action on living tissue and is specifically a fibrin dissolver. It is commonly used together with:

Streptodornase (Sd): Dornase is desoxyribonuclease which attacks nucleoproteins containing desoxyribonucleic acids. It appears to have no action upon living tissue when the nucleoprotein is protected by a cytoplasmic barrier. Dead cells with autolysis of the cytoplasm are further digested in the presence of this enzyme. Many bacteria which do not have a cytoplasmic barrier to the enzyme are killed and digested in its presence. Thus the combination of SkSd is capable of dissolving blood clots and also thinning and sterilizing purulent material.

Trypsin: This pancreatic enzyme was first isolated in crystalline form by Northrop and is now commercially available in a high degree of purity. It is a multipotent protein digestant acting either on the alkaline or acid side of neutrality but most powerfully at an alkaline pH. This substance is capable of digesting a large number of proteins although it does not specifically digest living cells as easily as non-living protein substrates. It is capable of digesting protein structures outside the cells with great ease. This is seen, for example, in an ileostomy where skin digestion, as a result of exposure of the skin surrounding the stoma to trypsin and intestinal proteolytic enzymes, is a very serious clinical problem. This enzyme is not normally found outside the digestive tract.

Pancreatic Dornase: This is another type of desoxyribonuclease relatively free from other pancreatic enzymes. Its action is similar to that of streptodornase except that it presents greater difficulty in preparation free from other enzymes. It is not normally found outside the digestive tract.

Hyaluronidase: This may be prepared from hemolytic streptococci or from the animal testis. This enzyme has a specific action upon hyaluronic acid which is a main constituent of the intercellular tissue cement. Thus it has been used most in improving methods of subcutaneous infusion of fluids. Its use has been relatively disappointing in those problems in diseases of the chest where enzymes have been considered. It has no action upon mucus or fibrin.

Other Enzymes: Papain is a wide-spectrum proteolytic enzyme of vegetable origin. It acts at an acid pH. It has been disappointing in therapeutic trial, although it is widely used in cancer cytology. *Lysozyme* is an enzyme specifically dissolving mucus and is normally found on surfaces upon which mucus is secreted. It is specifically mucolytic. Difficulty of preparation has prevented any widespread study of this enzyme.

CLINICAL USES OF ENZYMES

There is now considerable literature concerning the action of enzymes for clinical purposes. So far as diseases of the chest are concerned, these may be divided into diagnostic applications and therapeutic uses.

Diagnostic Applications. Proteolytic enzymes are used in cytologic studies. Sputums have been studied using trypsin or papain in the slide preparation. Although some advantage may be seen in such preparations, expense and time do not make this procedure as valuable as had been hoped. Another application is the use of enzymes on surfaces to facilitate desquamation of suspected malignant cells. This is at the moment difficult to evaluate. A neoplastic surface completely covered with fibrin and mucus may well appear to be negative for malignant cells on cytologic study. Dissolution of this covering would be important in increasing the number of early positive reports. This method is in routine use in the study of gastric secretions for malignant cells, using both the stomach's own proteolytic ferments and, in some cases, papain. The

intrabronchial use of a wide spectrum proteolytic enzyme requires further investigation.

Therapeutic Uses. The Intrapleural Use of Proteolytic Enzymes: Tillett and Sherry [*1*] originally described the use of SkSd in pneumococcal empyema, exudative pleurisy and clotted hemothorax. While they were impressed with the success of this treatment in these three conditions, in one case of postpneumonic empyema [*2*], liquefaction with SkSd was followed by extensive reopening of a bronchopleural fistula. Tillett, Sherry and Read [*3*] concluded that to utilize SkSd in patients with empyema or hemothorax with greatest effectiveness "enzyme therapy should be employed before the difficulties inherent in chronicity have become established." Since their original report in 1949 there have been reports of a number of series of cases in which SkSd or trypsin have been used intrapleurally in these conditions. Obviously, in clotted hemothorax it was believed desirable to avoid the necessity of opening the chest surgically to remove the clot. The organization of the pleural surfaces following pleurisy or empyema was amenable to treatment only by surgical decortication. If proteolytic enzymes provided an efficient, relatively non-toxic method of dealing with these conditions, it would be greatly to the patient's advantage. However, enzymes used this way are not devoid of risk.

Hopkins et al. [*4*] reported their experiences in thirty-four cases of chemical decortication. In twenty-three cases of traumatic clotted hemothorax, they observed satisfactory results in 87 per cent of the patients treated with SkSd; they likewise reported satisfactory results in four cases of clotted pleural effusion. In seven cases of empyema, however, there were only three satisfactory results in the early empyemas; in two cases SkSd instillation led to major hemorrhage and treatment was discontinued. The authors caution that hemorrhage is a major hazard in enzymatic debridement of empyema. Transient temperature rise is seen frequently following intrapleural instillation of SkSd or trypsin. Hubbard [*5*] reported on ninety local instillations of enzymes in twenty-eight patients. These patients had a variety of types of suppurative pleurisy or hemothorax. In almost every case he noted a febrile reaction with transient hematuria and albuminuria, although casts were few in the urine. Polymorphonuclear leukocytosis and an increase of sedimentation rate were also observed.

Creech et al. [*6*] report striking effectiveness of enzymatic agents in ten of sixteen cases of postpneumonectomy pleural space infections. Three of the four failures they reported were in chronic tuberculous empyema in which the pleural exudation was of long duration, with marked fibrous tissue organization. They found SkSd to be an adequate substitute for surgical intervention in fifteen of nineteen cases of hemothorax. However, they comment that "toxic responses are common during the course of enzymatic therapy and will generally coincide with the interval between injection and aspiration of the SkSd solution." Common toxic reactions were fever, often associated with malaise, leukocytosis and appearance of formed elements in the urine. These they controlled by administration of antipyretics and removal from the chest of the liquefied coagula within eighteen to twenty-four hours. Reiser, Roettig and Curtis [*7*] noted temperature elevation and suggested control of this apparent allergic reaction with benadryl.® They raised the point as to whether or not this reaction occurred because of the encroachment of the enzyme upon living tissue. On the other hand, Roettig et al. [*8*] and Morell and Weinberg [*9*] tend to minimize these toxic effects, dismissing them as self-limited.

There have been isolated case reports of severe febrile reactions followed such use of proteolytic enzymes. Whether this reaction is due to specific allergy or to toxic substances produced during proteolysis or nucleic acid degradation is not altogether clear. Both factors probably operate. Certainly both trypsin and SkSd are capable of producing specific allergy when introduced into the blood stream; and that they would be absorbed from a granulating surface is undoubted. Armstrong and White [*10*] found precipitins in the blood after using pancreatic dornase intratracheally. Johnson [*11*] showed the maximal outpouring of polymorphonuclear cells to occur twenty-four hours after injection of SkSd in human subjects. However, the febrile reactions appear commonly with the initial treatment, when antibody formation would not have occured. Anaphylactic responses to repeated treatments are difficult of assessment; they are uncommon but do occur. Cases reported by Baum and Oransky [*12*] and Goehring and Grant [*13*] illustrate both the unpredictability and seriousness of such responses.

The necessity for control of fluid formation after intrapleural instillation is particularly accentuated by Miller and Long [*14*], who report

serious displacement of the mediastinum as a result of fluid formation during the postinstillation period in patients with hemothorax who were treated with SkSd. This fluid formation may continue for several days and may comprise several liters of inflammatory exudate. As a result of this exudation, reloculation may occur. The necessity for rapid removal of the products of lysis and of any fluid which may form was emphasized by Read and Berry [*15*] in 1950 and by other authors since. In general, it is agreed that the enzyme, together with the products of lysis, must be removed within a few hours of administration. Otherwise, the effects of the digested fluid upon the granulating surface of the pleura may well be more serious than the original condition.

Bronchopleural fistula is one of the most important complications of the use of these agents. Many empyemas are originally produced by a bronchopleural fistula which allows the organisms to track from the lung into the pleural cavity. Often this bronchopleural fistula is transient, becoming plugged by fibrin and thus giving rise to an apparently completely closed empyema. The dangers of reopening a fistula are considerable, both because of the immediate complications of pyopneumothorax and the later complication of spread of disease from the empyema cavity to the lung. In almost every considerable series of cases in which these agents have been used in this way a significant number of bronchopleural fistulas have been reopened. Miller, White and Long [*16*] believe that tuberculous empyema with bronchopleural fistula is still accessible to treatment with enzymes but accent the care necessary in its management. They consider that non-tuberculous bronchopleural fistulas are not a contraindication to enzyme therapy but this is on the basis of only three cases. Razemon and Ribet [*17*], in a study of thirty-four cases, emphasized the importance of avoiding contact of the enzymes with granulating wounds or of recent sutures because of the danger of leaks. In our own experience pleurocutaneous leakage occurred in tuberculous empyema treated repeatedly with enzymes.

To summarize the use of intrapleural SkSd and trypsin in cases of empyema, exudative pleurisy and hemothorax, it seems that toxic reactions are common and that a definite risk exists in reopening a bronchopleural fistula, particularly in a patient with tuberculosis. Therefore, considerable caution must be used in exhibiting these drugs. Furthermore, there is general agreement with the viewpoint of Carr and Robbins [*18*] that enzyme debridement is no substitute for surgical decortication. The cases most suitable for enzyme debridement are those very cases in which a bronchopleural fistula is most likely to reopen, those in which organization of fibrous tissue on the pleural surface is not far advanced. Also, in these cases the pleural surface is covered with granulation tissue, with its excellent blood supply in contact with both the enzyme itself and the products of its lysis.

Read [*19*] reported on six patients in whom SkSd was instilled into the pleural cavity drainage tube immediately after resection of lung. He commented favorably upon this procedure, noting the easy control of fluid formation and the relative absence of loculated clots in the pleural space. However, caution is necessary. Creech et al. [*20*] warn against the dissolution of the fibrin clot at the end of the bronchus and consequent formation of bronchopleurocutaneous fistula. Since bronchopleural fistulas are not infrequent following resection of tuberculous lung tissue without the use of enzymes, it would seem somewhat dangerous to add to that risk by using enzymes postoperatively, in these cases at any rate. The serious nature of a bronchopleural fistula in an elderly patient who has undergone a resection of lung for carcinoma needs no emphasis. However, this aspect is not fully evaluated as yet.

Endobronchial Use of Enzymes. Muenster et al. [*21*] reported a case in which there was apparent speeding of resolution in pneumonia by endobronchial administration of SkSd. They noted some increased pyrexia with the treatment. Excellent results were likewise reported by Miller et al. [*22*] in two patients with slowly resolving pneumonia. They advise bronchoscopy in advance of administration of Sk, for detection of bronchogenic carcinoma, and caution against the use of SkSd in patients with active pulmonary tuberculosis to avoid possible bronchogenic spread of the disease. Steigman and Scott [*23*] treated 110 poliomyelitis patients with trypsin and thought that there was a considerable degree of liquefaction of mucus and consequently fewer pulmonary complications. Later Kofman et al. [*24*] reported similar treatment of tracheotomized patients in respirators. Seventeen patients were treated with aerosolized trypsin administered through a tracheotomy tube following which there was a decrease in the

viscosity of the tracheal secretion without changing the volume, percentage of sediment or nitrogen content. In sixteen patients treated with SkSd there was decreased sediment and viscosity, increased aspirate volume and decreased nitrogen concentration, the effect lasting at least four hours. The authors note the possibility of harming the patient with decreased tussive force or excessive secretions prior to treatment by the bronchorrhea which is induced by the streptococcal enzymes; they also note that even the decrease in viscosity following trypsin may be hazardous in similar patients by facilitating spread of material in the distal bronchi if adequate drainage cannot be established. Kofman et al. [*25*] also report on an additional twelve patients with acute poliomyelitis with tracheotomy in mechanical respirators in whom, although aerosol trypsin appeared to facilitate the aspiration of the secretions, there was no change clinically from those treated with normal saline aerosol. In six cases there was no favorable effect from aerosol SkSd and in three severe reactions occurred. They reported on twenty-one cases of direct instillation of trypsin into the tracheobronchial tree with adverse reactions in eleven patients including dyspnea, cyanosis, choking and burning sensations. They recommend that such direct instillations be used only into a bronchus of a known area of bronchial obstruction.

Peck and Levin [*26*] administered endobronchial trypsin to four patients with atelectasis, two of whom had poliomyelitis. The procedure used included aspiration first, then trypsin introduction, and aspiration after half an hour. "In the face of acute inflammation of the bronchial tree, some local tissue damage could occur causing local edema and superficial necrosis. It would perhaps be best not to use the drug in cases of acute tracheobronchitis." In their experience it was also contraindicated in patients with tuberculosis with bronchopleural fistula.

Salomon, Herschfus and Segal [*27*] report the use of pancreatic dornase in a variety of conditions in thirty-five patients with purulent, tenacious sputum and report a marked improvement of their condition on a short-term basis in a majority of the cases. There are a number of other favorable reports of this sort. With the use of aerosol trypsin there was an improvement in eighteen of twenty patients with heavy, thick, tenacious, respiratory secretion, according to Limber et al. [*28*]. They believed it to be relatively non-toxic, harmless to respiratory tissue and thought it did not retard ciliary action.

The French workers Biron and Choay [*29*] report results in eighty cases using aerosol trypsin for the relief of non-tuberculous bronchial obstruction. They reported excellent results in thirty-one of thirty-three cases of acute pulmonary collapse, twelve of fifteen cases of bronchiectasis, eight of eleven cases of asthmatic bronchitis, fifteen of twenty-one cases of bronchial asthma. They noted such side effects as temporary hoarseness, pyrexia, slight dyspnea or a temporary fall in blood pressure, which could usually be controlled or prevented by the use of appropriate antihistaminics. However, in seventeen cases of chronic bronchial asthma and chronic bronchitis Prince et al. [*30*] noted benefit in only two cases treated with preliminary inhalation of adrenalin followed by trypsin. Yates and Goodrich [*31*] treated seventeen patients with respiratory diseases unresponsive to usual therapy. Tryptic aerosol led to a decrease in the viscosity of sputum, promoted bronchial cleansing and was considered by them to be a helpful adjunct to usual therapy. Warnery et al. [*32*] used hyaluronidase together with streptomycin as an aerosol in pulmonary tuberculosis. They report a good response in fresh lesions. Britton and Habif [*33*] have reviewed the use of hyaluronidase as an aerosol; they do not believe that its usefulness in thinning bronchial secretions is established as yet. Unger and Unger [*34, 35*] report favorably on the use of trypsin inhalations to reduce sputum viscosity.

However, a note of caution was sounded by Farber and associates [*36*] who reported a significant amount of metaplasia seen in bronchial secretions over a long period of time after repeated endobronchial administration of trypsin aerosol. When dornase aerosol was used in treatment [*37*] they also found significant bronchorrhea in ten of twenty patients, together with several instances of severe dyspnea and one of bronchopleural fistula. These reactions appeared at about the tenth day and were presumed to be allergic. They also reported an increased incidence of lung tumors in a study series of seventy-two Strain A Heston mice over the natural expectancy when the animals were exposed to dornase inhalation over a prolonged period of time. (Fig. 1.) No such increased incidence was seen in the animals treated with trypsin. A later series of 270 mice (unpublished

FIG. 1. Typical pulmonary tumor observed in strain A Heston mice. This is a very regular benign-appearing tumor.

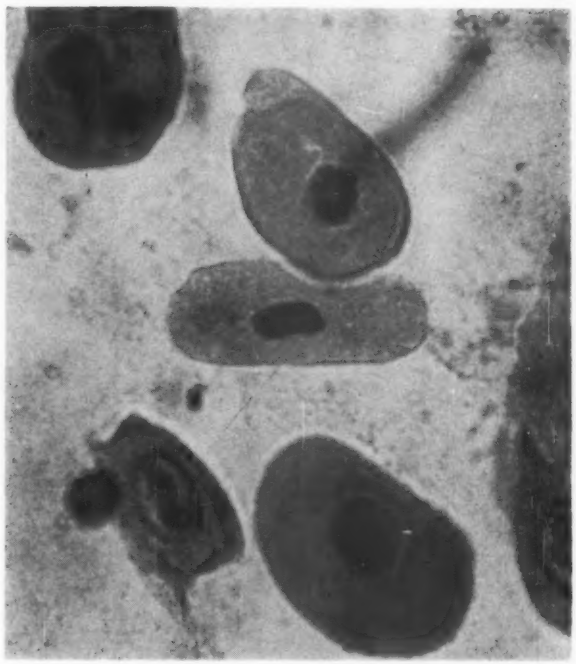

FIG. 2. Typical metaplastic cells in sputum of untreated patient.

data) sacrificed at six months confirmed the earlier report. The significance of these findings cannot of course be transferred to human studies (Figs. 2 and 3) but the authors believe that as yet neither trypsin nor dornase should be used as aerosols for prolonged therapy. Habeeb et al. [*38*] are less impressed with the importance of the metaplasia.

It is evident that a great deal more careful research in this field is required. The seriousness of plugging of respiratory passages by tenacious, purulent sputum needs no emphasis and an agent capable of liquefying these secretions is greatly needed. There is as yet insufficient evidence of the desirability of administration of proteolytic enzymes in all cases to justify their routine use by aerosol or instillation into the tracheobronchial tree.

Parenteral Use of Trypsin. This has been reported by several authors. Using purified intravenous trypsin, Innerfield, Angrist and Schwartz [*39*] reported subsidence of acute inflammation in local sites. They described [*40*] the parenteral use of trypsin in 538 patients with acute inflammatory reactions; in their experience there was rapid suppression of acute inflammation of whatever cause. Purified trypsin preparations suitable for intravenous administration are available with very little tendency to produce allergy although mild side reactions frequently occur. The rationale of treatment with intravenous trypsin is that lysis of the fibrin walling off the infection from the host may be accomplished, thus improving the blood supply in the region of inflammation. The prothrombin time rises. This type of therapy requires further study before such treatment can be accepted as completely desirable. The application of such therapy to the treatment of cavitary tuberculosis is made hazardous by the possibility of hemorrhage. Babich [*41*] reports excellent results in cases of exudative pleurisy and empyema treated by direct introduction of lysogland into the pleural cavity; the exudates rapidly decreased. This substance was also used parenterally in fifteen patients with pulmonary tuberculosis with apparent therapeutic response and little toxicity. Shingleton et al. [*42*] reported the experimental use of intravenous trypsin in pulmonary embolism in the dog.

The Use of Enzymes in Sinus Tracts. The use of enzymes to prevent loculation and persistence of sinuses has been studied to a considerable extent. Here the disadvantages of fluid formation and of retention of products of lysis are minimized. Miller et al. [*43*] report sixteen excellent and three good results in nineteen patients with infected wounds which they treated with tryptar® in combination with the indicated surgery and

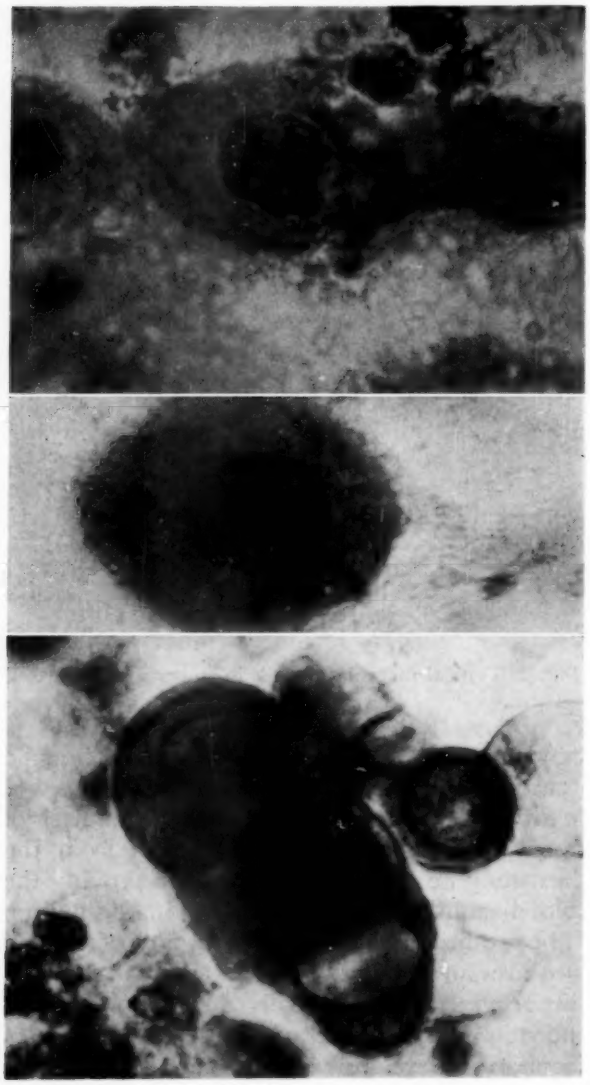

FIG. 3. Atypical metaplastic cells observed in sputum of patients treated with trypsin inhalation.

antibiotics. Castigliano and Rominger [*44*] reported further ulceration in a case of indolent postroentgen radiation ulcer, following use of SkSd. Reiser et al. [*45*] report the great effectiveness of trypsin in the debridement of infected necrotic wounds.

Numerous well known reports of the treatment of purulent wound surfaces with proteolytic enzymes will not be discussed here. However, toxic reactions can occur and wound healing may actually be delayed. Most tuberculous sinus tracts are amenable to chemotherapy today and the need for enzyme debridement of the tract appears to be much less than it was thought to have been. In patients with bronchopleural-cutaneous fistula it is believed that the risks of therapy are considerable and the approach remains essentially surgical.

SUMMARY

The initial enthusiasm with which enzyme therapy was greeted must now be tempered with caution. Although excellent results have been obtained with application of various enzymes in diseases of the chest, toxic manifestations both immediate and delayed have become numerous enough to give us pause in the routine use of these agents.

The main problems to be resolved in enzyme therapy appear to be the following:

1. Enzymes used clinically at present are derived from non-human sources and are applied to sites in which such substances would not normally occur. They may give rise to antibody formation with occasional marked hypersensitivity causing severe local and systemic disturbances.

2. The enzymes themselves or the products of lysis produce local and systemic reactions of varying severity in almost all patients, depending upon dosage and route of administration.

3. Late toxic effects upon epithelium have been seen in the tracheobronchial tree.

4. The dissolution of fibrin plugging a bronchopleural fistula or a vessel gives rise not infrequently to hydropneumothorax or severe hemorrhage.

Prediction of success or complication in the therapeutic application of enzymes is not now possible. Serious complications may occur early and it is necessary carefully to calculate the risks when enzyme therapy is proposed. This is not to suggest that enzyme therapy should only rarely be employed, but to emphasize the powerful nature of these agents and the dangers in their indiscriminate use.

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Seminar on Bone Disease

Rickets and Osteomalacia*

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BONE consists of a bone matrix in which calcium and phosphorus are deposited. The bone matrix is composed chiefly of a protein – collagen – and of carbohydrates [*1*]. Collagen is characterized by the presence of hydroxyproline and hydroxylysine and by the absence of cystine, cysteine and tryptophane. The carbohydrates of the bone matrix are polymucosaccharides among which chondroitin, chondroitin sulfate and hyaluronic acid are the most noteworthy.

Bone formation results from the precipitation of a special form of calcium phosphate, so-called hydroxyapatite, within the bone matrix. In rickets and osteomalacia the formation of bone matrix is normal, but calcium or phosphorus, or both, are not available for precipitation within the bone matrix. Each day a small amount of bone substance is resorbed which represents the so-called normal wear and tear of the skeleton. This resorption of bone must be compensated for by the deposition of an equivalent amount of bone substance. If calcium phosphate is not available for deposition in the bone matrix then, due to the daily wear and tear, the calcium stores of the skeleton are gradually depleted. The resulting bone disease is designated as rickets in children and osteomalacia in adults. In these conditions the non-calcified bone matrix is visible at histologic examination in the form of broad osteoid zones around the bone trabecules.

In rickets the epiphyseal disks reveal clear-cut changes in the form of swelling and irregular proliferation of the cartilage within the disk, especially at the metaphyseal border. In the costochondral junctions of the ribs of both adults and children, bone and cartilage are adjacent. Here the same proliferation of cartilage takes place as occurs in the epiphyseal disks of rachitic children. The resultant costochondral swelling, known for many decades as the "rachitic rosary," is common to osteomalacia and rickets.

Ultimately, both in rickets and in osteomalacia the amount of calcium phosphate contained in the bone substance diminishes. This at x-ray examination presents as generalized resorption of bone substance. The resorption is more marked in osteomalacia than in rickets, allegedly because in the younger age groups the insufficient formation of trabecular bone is balanced by excessive formation of fiber bone. In adults fiber bone is not as easily formed as in children. Symmetric narrow fissures in the cortex of bone, so-called Milkman's pseudo-fractures [*2*], are characteristic of osteomalacia, at least if no other bone disease is present [*3*]. It is likely that these fissures represent incomplete fractures with excessive formation of osteoid [*4,5,6*].

In both diseases the serum calcium and phosphorus are low, the serum alkaline phosphatase is increased. The urinary calcium excretion is minimal, but the phosphaturia is not diminished.

RICKETS AND OSTEOMALACIA DUE TO AVITAMINOSIS D

Both rickets and osteomalacia may be caused by insufficient intake of vitamin D. This occurs when the diet is devoid of animal food; a completely vegetarian diet contains no vitamin D. Since vitamin D is formed in the skin under the influence of sunshine, avitaminosis D is extremely rare in sunny climates irrespective of diet. Excessive losses of vitamin D in the stool, and occasionally excessive losses of calcium and/or phosphate in the urine, may cause rickets and osteomalacia. The latter occurs in certain dysfunctions of the renal tubules.

Insufficient intake of calcium alone hardly ever plays a role in the causation of rickets and osteomalacia, except in conditions in which the requirements of calcium are excessively high, as is the case in pregnancy and lactation.

Physiology of Vitamin D. In the absence of

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vitamin D, calcium is not absorbed from the intestine. Contrariwise, increasing amounts of vitamin D render the absorption of calcium almost complete. Positive calcium balances can easily be maintained on low calcium diets if sufficient vitamin D is given. In addition to promoting calcium absorption from the intestine, vitamin D has other functions [*1*].

Vitamin D, like parathyroid hormone, allegedly increases the phosphorus excretion by the kidneys by inhibiting the reabsorption of phosphorus in the proximal renal tubule. This view, however, is an oversimplification and deserves serious re-evaluation. Although in parathyroidectomized animals phosphaturia increases under the influence of vitamin D, this does not occur in animals with intact parathyroids. As a matter of fact, Crawford and his associates recently came to the conclusion that in normal animals vitamin D and parathyroid hormone have opposing actions on the renal tubular reabsorption of phosphate [*7*]. Furthermore, it is well established that large doses of vitamin D will augment tubular reabsorption of phosphate in certain tubular disorders which are characterized by hyperphosphaturia.

The possibility that vitamin D also influences the excretion of calcium in the urine must be considered. In the initial stages of avitaminosis D the serum calcium hovers at the lower limits of normal (8.5 to 9.0 mg. per cent). The calcium of the urine dwindles to traces whereas in normal persons a low normal serum calcium is associated with the excretion of considerable amounts of calcium.

The curative action of vitamin D in rickets and osteomalacia may not be limited solely to correction of the abnormal levels of calcium and phosphorus in the serum and urine. Experimental beryllium poisoning causes bone changes which are highly reminiscent of rickets. In such animals the serum phosphorus decreases, due to the formation of non-absorbable beryllium phosphate in the intestine. The decrease of serum phosphate alone is not the cause of the arrest of enchondral calcification. When under influence of the administration of vitamin D to animals with beryllium poisoning the hypophosphatemia disappears, the changes in the epiphyseal disks persist. It therefore seems probable that beryllium has an unfavorable influence upon enzymatic processes which are necessary for the ossification of the epiphyseal disks. It seems possible that avitaminosis D may have a comparable influence upon the ossification of the epiphyseal disks.

Finally, vitamin D also increases resorption of bone [*8*]. This becomes evident in hypervitaminosis D, both in experimental animals and in man. In human subjects especially, hypervitaminosis D always leads to marked generalized resorption of bone and to metastatic calcification.

In osteomalacia and rickets, due to avitaminosis D, the impaired absorption of calcium from the intestine is the main cause of the skeletal changes. The rachitic changes in the epiphyseal disks can perhaps be partly ascribed to a modification of the enzymatic processes which under the influence of vitamin D lead to enchondral calcification.

Rickets and Osteomalacia Due to Insufficient Intake of Vitamin D and Insufficient Exposure to Sunshine. Considering the calcium requirements in general, many nutritionists are of the opinion that daily food should contain 800 mg. of calcium in order to safeguard health. However, when vitamin D is available even a small daily intake of calcium, 300 to 400 mg., is sufficient to keep the calcium stores of the skeleton intact [*9–11*]. On the other hand, in the absence of vitamin D and/or sunlight no amount of calcium will prevent exhaustion of the calcium stores of the skeleton because all the calcium of the food, whether large or small in quantity, appears in the stools. On the contrary, intake of large amounts of calcium salts without vitamin D is decidedly unfavorable for the mineral metabolism. In avitaminosis D the intestinal absorption of calcium is practically nil, but the absorption of phosphorus is normal. Thus the urine of such patients, although free of calcium, contains normal amounts of phosphorus. If such a patient with avitaminosis D receives large amounts of calcium salts, the latter remain in the intestine and form insoluble calcium phosphate. Phosphorus no longer is available for absorption and the phosphorus content of the urine dwindles to traces. Cow's milk, which contains large amounts of calcium and even larger amounts of phosphorus, is therefore a nutrient which favors calcium absorption only when the milk also contains vitamin D. Fortunately in our country nowadays all the milk is vitaminized. Years ago, milk obtained from cows which were kept in stables during the winter was practically devoid of vitamin D; only during the summer when the cows were in the meadows did the milk contain

this vitamin. Thus, during the winter the children did not receive any vitamin D, the serum calcium went down to tetany levels, and tetany developed in the rachitic children in the early spring. At that time, when vitamin D was not known, the most efficient treatment for tetany consisted of prohibiting the administration of any milk. This treatment prevented the administration of a nutrient without vitamin D but with large amounts of phosphorus, which exceeded the quantity of the calcium.

Rickets and osteomalacia are cured by the daily administration of 5,000 to 10,000 units of vitamin D, irrespective of a high or low calcium or phosphorus diet. It is also immaterial whether the calcium : phosphorus ratio of the diet is high or low. In contrast to cow's milk, breast milk contains twice as much calcium as phosphorus and both concentrations are low.

Although adults can remain healthy with a low calcium intake of approximately 300 mg. per day if the administration of vitamin D is sufficient, this does not hold true for pregnant and lactating women. During pregnancy a calcium intake ordinarily adequate for calcium balance is no longer sufficient to maintain the calcium stores of the skeleton of the patient, due to the diversion of large amounts of calcium to the growing fetus. Calcium balance studies made during pregnancy must take into consideration the fetal needs before a satisfactory intake of calcium is prescribed. Studies with radioactive calcium have proved that calcium atoms are freely and rapidly transferred through the barrier of the placenta from the maternal to the fetal organism. It must be noted that this transport of calcium is accomplished against a gradient; the fetal plasma calcium, especially the ionized moiety, is higher than the calcium content of the maternal plasma. The avidity of the fetal bones for calcium may well be an important factor in the migration of calcium from the maternal to the fetal circulation against this gradient. In this respect it should be mentioned that considerable amounts of calcium are present in the placenta.

The following data illustrate these points [*1*]. The skeleton of the newborn contains 21 to 23 gm. of calcium and 14 gm. of phosphorus. In exceptional cases the calcium content of the skeleton of the newborn has been found to amount to 30 gm. It has been calculated that in order to keep the maternal skeleton intact the pregnant woman must retain 50 mg. of calcium daily in the third, fourth and fifth lunar months of pregnancy, 120 mg. in the sixth, seventh, eighth and ninth months and 450 mg. during the tenth month. Other authors have expressed the opinion that in order to protect her skeleton, the pregnant woman must retain a daily minimum of 200 mg. of calcium and 100 mg. of phosphorus during the last three months of pregnancy.

Lactation imposes a still heavier drain on the calcium stores of the maternal skeleton. The calcium content of human breast milk varies between 25 and 30 mg. per cent. During the first few months of lactation when 1,000 to 1,200 cc. of milk are produced daily, 300 to 400 mg. of calcium will be lost in the milk. Unless this quantity is replaced the maternal skeleton will be drawn upon.

During pregnancy the calcium intake must at least cover the quantity of calcium removed in the stool and urine, plus the estimated amount required for calcification of the fetal skeleton. During lactation the calcium intake must cover the calcium lost in urine, stool and milk. In other words, in order to satisfy the needs of pregnant women, a daily intake of 1,000 mg. of calcium is necessary, even in population groups who are accustomed to a low calcium intake under normal conditions. The lactating woman may need 1 to 2 gm. of calcium daily; in order to absorb this amount of calcium both pregnant and lactating women of course need a sufficient amount of vitamin D.

The growing infant needs a large amount of calcium because it must deposit considerable quantities of calcium in its skeleton. Breastfed infants receive 300 to 350 mg. of calcium daily, of which 76 to 82 per cent must be retained in order to maintain a positive calcium balance [*12*]. All this is easily possible if the mother receives a sufficient amount of vitamin D. If the mother suffers from osteomalacia the calcium intake of the child does not suffer, because in this disease the calcium content of the breast milk is not reduced. However, such a breastfed child does not receive any vitamin D with the mother's milk. The child then suffers from rickets because the calcium derived from the breast milk is not absorbed from the intestine of the infant. There is little likelihood of this happening in the Western part of the world. However, in the sunless part of the Far East and in the seraglios of the Mohammedan world rickets of the newborn does occur [*13*].

In our part of the world rickets and osteomalacia have become rarities, since the diets have a satisfactory content of vitamin D, and exposure to sunshine has become a national habit. This, however, does not hold true for other continents. Although both in North and South China the diet for all practical purposes is purely vegetarian, in tropical South China the continuous exposure to sunshine prevents the development of rickets and osteomalacia. The same diseases are frequent in several provinces of North China, especially in the provinces of Hopei and Shensi, where sunshine is less abundant than in tropical China. In most areas of India osteomalacia is also rare. In Kashmir, however, osteomalacia developed in the rich Mohammedan women who were kept in seraglios and hardly ever were allowed to walk in the sunshine. In the same area women of the lower economic levels worked as boat women. These women, who hardly ever suffered from osteomalacia despite their reduced vitamin D intake, were exposed to the protective effects of the sunshine [*14*].

The poor population of North China lives on a purely vegetarian diet with a daily calcium intake of about 250 mg. [*9*]. This is a satisfactory calcium intake for the peasants who, for the greater part of the day work out of doors and thereby manufacture a sufficient amount of vitamin D in the skin. In the cities the women are kept within the houses by their many household duties and are always on the verge of osteomalacia. Loss of calcium during menstruation, and especially losses of calcium during pregnancy and lactation, are sufficient to cause frank osteomalacia. The latter disease is rare among the men who are more frequently exposed to the sunshine.

Until thirty years ago infantile rickets was a common disease in the Western part of the world. During the latter part of the nineteenth century and the first thirty years of the twentieth century, when infantile rickets was rampant, the pregnant American and European woman had a satisfactory diet, especially a satisfactory vitamin D intake. In these areas the pregnant mother could provide the growing fetus with a satisfactory vitamin D supply, and at birth the newborn had sufficient stores of vitamin D to last for approximately six months. During that era fear of intestinal infections of newborns was prevalent and the milk which was the mainstay of the infantile diet was sterilized. This destroyed most of its scanty vitamin D content, thus the diet of the infant was practically free of vitamin D. Infants were usually kept inside, or if they were allowed in the open they were heavily dressed; usually, only the tip of the infant's nose was visible. The newborns gradually exhausted the vitamin D supply with which they were born, and after six months signs of avitaminosis D developed in the form of rickets. During the next year or eighteen months the diet was still restricted and consisted mainly of milk, porridge and other easily digestible carbohydrates. Rickets therefore persisted until the age of two when the children were allowed a more liberal diet and began to romp freely out of doors in the sunshine. Since it was well known that cod liver oil had a curative influence upon rickets, in retrospect it can hardly be understood why nobody was clever enough to prescribe small amounts of cod liver oil prophylactically. This would immediately have terminated the endemic of rickets which involved nearly all artificially fed children. The breast fed children suffered much less from rickets than children who were fed with cow's milk. The mother's milk was of course not sterilized and the milk of the mothers who had a mixed diet contained sufficient amounts of vitamin D.

This experience points up the fact that the calcium content of the diet is of little importance for the prevention or cure of rickets. These children who were overfed with milk were, if anything, on a calcium-rich diet. Cow's milk contains even more calcium than mother's milk. Although the children fed with cow's milk had a much higher calcium intake than the children fed with mother's milk, rickets developed in the former but not in the latter.

As occurs in all conditions with longstanding hypocalcemia, rickets and osteomalacia are associated with secondary hyperplasia of the parathyroid glands [*13*]. Several authors have considered the possibility that this secondary hyperplasia might result in secondary hyperparathyroidism. Since in avitaminosis D hypophosphatemia is a frequent occurrence, the decrease of the serum phosphorus has been interpreted as a sign of hyperparathyroidism. As a matter of fact, parathyroid hormone inhibits the reabsorption of phosphorus by the convoluted tubules, resulting in hyperphosphaturia and hypophosphatemia. It has already been mentioned that ingestion of large amounts of calcium salts by patients with rickets and osteomalacia changes the normal phosphaturia to hypophosphaturia.

This does not occur if large amounts of calcium salts are given to patients with true hyperparathyroidism. As already mentioned, Crawford and his associates [7] ascertained that vitamin D has an antagonistic effect on phosphate reabsorption when compared with parathyroid hormone. Thus, in the absence of vitamin D the action of the normal amount of parathyroid hormone may be excessive. The hypophosphatemia in avitaminosis D could therefore be due to the unopposed action of physiologic amounts of parathyroid hormone on the renal tubule.

Osteomalacia and Rickets Due to Fatty Diarrhea. In many – but not all – cases of fatty diarrhea, rickets and osteomalacia may appear. It should be added that in some cases, osteoporosis may also develop. In osteomalacia the bone trabecules are surrounded by broad osteoid borders, in osteoporosis the bone trabecules are thin and wide osteoid seams are not found. In osteomalacia the bone matrix is normally formed but calcium phosphate is not available for deposition. In osteoporosis no bone matrix is formed because the synthesis of matrix protein is impaired and no bone can be formed even in the presence of normal amounts of calcium phosphate. Finally, in contrast to the characteristic biochemical findings in rickets and osteomalacia, the calcium, phosphorus and phosphatase contents of the blood serum and the urinary calcium are normal in osteoporosis.

It has already been emphasized that osteomalacia is not due to an insufficient calcium intake but to the absence of vitamin D. In fatty diarrhea the losses of vitamin D are also more important than the losses of calcium.

Rickets and osteomalacia are found in celiac disease, in non-tropical sprue, in chronic obstructive jaundice and in chronic biliary fistulas [15]. These conditions must be present for at least two years before the skeletal abnormality develops.

In celiac disease and in non-tropical sprue the absorption of fats and fatty acids by the intestinal wall is impaired. Fat-soluble vitamin D also is not absorbed and is eliminated in the stools. Thus patients with celiac disease and with non-tropical sprue suffer from avitaminosis D which in children with celiac disease presents as rickets [16] and in adults with non-tropical sprue as osteomalacia.

In obstructive jaundice and in biliary fistula no bile and therefore no bile acids reach the intestine. The bile acids are of great importance for fat absorption because they bring about the emulsification of the fatty substances. In the absence of this emulsification fats—also vitamin D—are not absorbed and again avitaminosis D results.

It cannot be denied that in celiac disease, non-tropical sprue, chronic obstructive jaundice and biliary fistula large amounts of calcium are lost in the stool. In all these conditions normal amounts of pancreatic juice are excreted into the intestine. Pancreatic lipase splits the neutral fats within the small intestine into fatty acids and glycerol. The excess fatty acids carry large amounts of calcium and magnesium soaps out with the stool. This, however, is no major factor in the pathogenesis of rickets and osteomalacia. It is possible to stop the loss of calcium in the stool in these conditions by the administration of moderate amounts of vitamin D but the osteomalacia and rickets persist [17].

In contrast to the marked skeletal lesions which occur in the conditions mentioned, no bone lesions appear in patients with longstanding diarrhea due to pancreatic disease. This holds true for children with cystic fibrosis of the pancreas, so-called mucoviscidosis [18]. In this condition no pancreatic juice reaches the intestinal lumen and in the small intestine no fatty acids are formed from the neutral fats. Since the small intestine does not absorb neutral fats but only fatty acids, in this disease the fat absorption is practically zero. The absorptive powers of the intestinal wall are not impaired and fat-soluble substances like vitamin D can be absorbed without difficulty [1]. Fecal excretion of calcium is moderately increased, because calcium soaps are formed in the large intestine in which the neutral fats are split by bacterial action. However, these fatty acids also are lost in the stool, because no fats or fatty acids are absorbed in the colon. Thus, patients with pancreatic insufficiency can freely absorb vitamin D and do not suffer from rickets or osteomalacia.

In patients with chronic fatty diarrhea, in addition to osteomalacia, typical osteoporosis may develop [19,20]. In women with chronic fatty diarrhea the estrogen levels of the blood are often decreased and estrogen deficiencies have an unfavorable influence upon protein synthesis. This may well lead to osteoporosis.

Since in sprue-like syndromes and in fatty diarrheas due to obstructive jaundice and biliary fistulas the skeletal anomalies are due to non-absorption of vitamin D, oral administration of

vitamin D is often without effect upon the disease. Parenteral administration of very large doses of vitamin D—50,000 to 300,000 units daily—[*20*], or better still, exposure to the sun or to ultraviolet radiation can be used to interrupt the vicious cycle which results from the non-absorption of vitamin D in these forms of fatty diarrhea.

VITAMIN D – RESISTANT RICKETS AND OSTEOMALACIA IN RENAL TUBULAR DISORDERS

The renal lesion present in most kidney diseases encountered, *viz.*, in chronic glomerulonephritis, pyelonephritis and vascular renal disease, produces reduced glomerular filtration. In such cases the biochemical syndrome of uremia with its inevitably associated acidosis will, if present long enough, evoke extensive skeletal lesions. In the main, the histologic appearance of the bones in such patients with longstanding chronic uremia and acidosis is that of osteitis fibrosa.

In a less commonly encountered group of patients with renal disease impairment of tubular function is in the foreground and uremia caused by glomerular dysfunction is either absent or is only a late manifestation. In this group of "renal tubular dysfunctions" [*21,22,23*] disease of the skeleton is frequently present. In these cases osteitis fibrosa usually does not develop, but roentgenologically and histologically the bone lesions resemble rickets and osteomalacia.

The renal tubular network comprises approximately 6 square meters of surface area through which the kidney is able to reclaim the vast amounts of electrolytes, amino acids, vitamin C, glucose and water present in the 170 L. of ultrafiltrate which pass through the glomeruli daily. When required, the renal tubule implements the acid-base regulatory mechanism of the body by varying bicarbonate reabsorption and by adding ammonia and acid to the distal tubular urine. When the potassium and the creatinine content of the plasma are increased, the human renal tubule may secrete these two substances.

In the proximal convoluted tubule all the glucose [*24*] and the greater part of the phosphates and amino acids of the ultrafiltrate are reabsorbed. Impairment of the proximal part of the tubular apparatus may result in varying degrees and combinations of disturbances in the reabsorption of these substances. In certain congenital and acquired disease entities any or all of these substances may be present in excessive quantities in the urine as the only manifestation of impaired renal function.

Isolated disturbances of distal tubular function also occur and present an entirely different biochemical and clinical syndrome. In the distal tubules the kidney elaborates a concentrated urine by completing the reabsorption of water and electrolytes, and contributes to the over-all base economy by manufacturing and substituting ammonia and hydrogen ions for fixed base. When suitable conditions prevail, potassium and creatinine are secreted directly from the blood into the distal tubular urine.

Three different forms of renal tubular dysfunction, all leading to skeletal anomalies resembling rickets or osteomalacia, can be distinguished. While in most of these cases it would appear that a disturbance of either the proximal or the distal tubule predominates, it has become evident that disturbances of both the proximal and distal part of the tubular system can usually be demonstrated [*25*].

"*Phosphate-Diabetes.*" Fanconi and Girardet [*26,27*] described a form of proximal tubular dysfunction in which excessive renal loss of phosphate forms the predominating biochemical disturbance. They called this condition "phosphate diabetes," meaning excessive urinary loss of phosphate. This disease bears no relationship to diabetes mellitus although in many cases of phosphate diabetes so-called renal glucosuria (without hyperglycemia) also is present.

Impairment of phosphate reabsorption by the proximal tubule in these cases results in tremendous urinary losses of this electrolyte. The serum phosphorus falls to low levels and, as is frequently observed in hypophosphatemia, excessive excretion of calcium via the intestine, with ensuing hypocalcemia, results. The net effect is diminished availability of phosphate and calcium for normal ossification of the bone matrix. In children, rickets and in adults, osteomalacia must necessarily result. In both diseases broad osteoid borders are found. In addition, in rickets the epiphyseal disks fail to calcify and become abnormally wide. The metaphyseal ends of the epiphyseal disks are markedly fuzzy due to excessive proliferation of the epiphyseal cartilage.

About forty cases of rickets and osteomalacia due to phosphate diabetes have been reported [*28,29*]. The etiology remains obscure but appears to be associated with a congenital defect

of the proximal tubular function. The disease is hereditary and probably represents a dominantly inherited trait.

As early as 1918 Gould pointed out that patients with neurofibromatosis of von Recklinghausen often suffer from osteomalacia [*30*]. It has recently been reported [*31*] that this generalized resorption of bone occurring in neurofibromatosis is a manifestation of phosphate diabetes. Both von Recklinghausen's bone disease and phosphate diabetes are hereditary conditions which apparently may occur together. It is interesting that Milkman's original patient with pseudo-fractures actually suffered from phosphate diabetes.

The signs, symptoms and roentgenologic features of phosphate diabetes cannot be differentiated from rickets and osteomalacia due to avitaminosis D. The difference lies in the response of these two conditions to therapy with vitamin D. Whereas patients with rickets and osteomalacia due to lack of vitamin D respond to relatively small doses of this vitamin (3,000 to 5,000 units daily), such doses have little or no effect upon patients with phosphate diabetes. For this reason the latter disease is designated as "vitamin D-resistant." Massive doses of vitamin D (50,000 to 100,000 units daily, sometimes even 1 million units), on the other hand, sufficiently increase renal tubular reabsorption of phosphate to improve the bone condition. It is known that vitamin D activates the alkaline phosphatase present in the renal tubules [*32*]. This enzyme, believed to be involved in the tubular transport of phosphate, is present in diminished amounts in the kidneys of patients with phosphate diabetes. Massive vitamin D therapy may therefore owe its beneficial effects to the potentiation of such a depleted enzyme system.

Whenever such massive vitamin D administration is required the dangers of generalized resorption of bone must be borne in mind; metastatic calcification in the kidneys, heart and other visceral organs cannot always be avoided.

Male hormone, which allegedly causes an hypertrophy of the renal tubules, has been of some value in the treatment of this disorder [*33,34*].

Lignac-Fanconi's Syndrome. In 1924 Lignac [*35*] described two children with severe rickets, dwarfism, renal disease and extensive cystine deposits in various tissues. He ascribed this condition to altered protein synthesis, connected with the disturbed cystine metabolism. He further hypothesized that the renal lesion was due to cystine deposition in the kidney parenchyma [*36,37*]. In 1933 DeToni [*38*] described a comparable case. In 1934 Debré [*39*] observed increased urinary excretion of organic acids in other such patients. In 1936 Fanconi [*28,29*] observed hyperphosphaturia and hypophosphatemia in these patients and advanced the concept that this disorder resulted from impaired tubular reabsorption of phosphate. He also reported associated defects in the reabsorption of glucose and probably of amino acids. McCune [*40*] later confirmed the aminoaciduria which exists in this disease. This investigator reported that the daily excretion of amino acids could rise to as high as 8 gm.

While, in the main, the tubular defect in Lignac-Fanconi's syndrome appears to reside in the proximal tubule, some subjects have associated disturbances of the distal tubule resulting in excessive cation losses and acidosis.

In the children with Lignac-Fanconi's syndrome, just as in phosphate diabetes, the hyperphosphaturia results in a decreased availability of mineral substances for normal calcification of bone matrix. These patients, also designated as vitamin D-resistant, respond only to massive doses of this vitamin.

The first signs of this disorder are polydipsia, polyuria and anorexia. These children are irritable, have frequent episodes of vomiting, alternating constipation and diarrhea, and signs of rickets are always found. Glucosuria without hyperglycemia is nearly always present, frequently associated with mild ketonuria [*41*]. Paper chromatographic studies have revealed that twenty different amino acids may be present in the urine. The aminoaciduria varies qualitatively and quantitatively from case to case.

Due to the hyperphosphaturia, the serum phosphorus is nearly always low. The serum calcium is usually normal but may be low, especially if a distal tubular defect is also present. Such patients frequently eliminate an alkaline urine rich in calcium. In most cases the ability to secrete ammonia is remarkably well preserved. The serum bicarbonate is frequently low, especially in patients with an alkaline urine. The alkaline phosphatase content of the serum is usually elevated.

The disease begins early in life and affected children usually die before puberty. Death is caused by intercurrent infections, episodes of

muscular weakness and lethargy, uremia or vasomotor collapse. The presence of hypopotassemia in some cases may be responsible for the neuromuscular and vasomotor fatalities [*21,22*].

Whereas cystinosis is frequently observed in this disorder, cystinuria is uncommonly present. Lignac-Fanconi's syndrome must therefore be differentiated from the more common disorder, cystinuria, in which cystine nephrolithiasis is frequent, but cystine deposits in visceral organs are never observed. Such patients also excrete excessive quantities of other amino acids, specifically lysine, arginine and ornithine. However, hyperphosphaturia is absent, and skeletal disease does not occur. Cystinuria with nephrolithiasis has a relatively benign course.

The disorder in the Lignac-Fanconi's syndrome has been ascribed to anatomic and enzymatic defects in the renal tubule. Examination of teased nephrons from such patients has revealed an abnormally short proximal convoluted tubule connected to the glomerulus by a remarkably long and narrow "swan-like" neck [*42*]. The alkaline phosphatase in the renal tubule has been found absent, as occurs also in phosphate diabetes. This favors the assumption that effective reabsorption of glucose and phosphate might result from impaired phosphorylation in the renal tubule. The aminoaciduria cannot be explained solely by a tubular defect because the amino acid content of the serum may be increased. This finding and the widespread cystinosis present in many patients suggests the possibility of multiple enzymatic defects. Perhaps this disease presents, as Lignac suggested, a disorder of the intermediary metabolism of amino acids. Stowers and Dent [*43*] believe that simple Mendelian transmission is involved; the full-blown form is present in homozygous persons while the incomplete types are present in heterozygous persons.

The problem of Lignac-Fanconi's disease in adults has recently been reviewed [*4,44*]. In these patients generalized cystinosis does not occur but a moderate degree of distal tubular dysfunction is usually present. These patients therefore usually have mild systemic acidosis, alkaline urine excretion and hypercalcemia in addition to the glycosuria, hyperphosphaturia and aminoaciduria. The rare association of this disorder [*44–46*] with multiple myeloma has been observed.

As already mentioned, massive doses of vitamin D are required to exert a salutary effect on the skeletal disorder. Intercurrent infections require early institution of appropriate antibiotic therapy. In those subjects with an associated distal tubule disorder, alkalinizing mixtures (Shohl's regimen) with supplemental potassium salts will also be necessary to correct the associated acid-base and electrolyte defects. The addition of sex hormones, especially testosterone, should be tried in view of their reported beneficial effects on tubular function [*33,34*].

Hyperchloremic Tubular Acidosis. The biochemical disorder of hyperchloremic acidosis may be iatrogenically induced or arise secondarily from alterations in the distal renal tubule. This latter entity is referred to as Butler-Albright's syndrome or Albright-Lightwood's syndrome [*47*].

It will be recalled that the function of the distal tubule, in addition to completing the reabsorption of electrolytes and water begun in the proximal tubule and thin limb or Henle's loop, is unique in that ammonia production and the elaboration of an acid urine is accomplished at this site. Dysfunction of this organ therefore may result in a diuresis of large amounts of water and essential cations (sodium, potassium, calcium) associated with profound disturbances in the acid-base balance of the body.

The voluminous urine of such patients is usually of low specific gravity, alkaline, very low in ammonia and rich in cations such as sodium, potassium and calcium. It is generally known that when bicarbonate is not available for reabsorption the renal tubule maintains total anion reabsorption nearly constant by augmenting chloride reabsorption. Since patients with this disorder have no defect in chloride reabsorption, prolonged bicarbonate losses in the urine evoke the biochemical pattern of hyperchloremic acidosis. Occasionally, a low serum potassium is also present [*16*]. The tendency to develop a low serum calcium is probably counteracted by mobilization of calcium from the bone, due to the acidosis.

Such a metabolic alteration can readily be produced in patients treated for other disorders by the administration of acidifying salts such as ammonium chloride and calcium chloride, and after prolonged diamox® therapy.

When this disturbance is not drug-induced it is believed to arise from alterations in the function of the distal tubule. Hyperchloremic tubular acidosis has been observed in infants, children and adults. The earlier the onset, the graver

is the prognosis. The etiology remains obscure. In some cases the defect appears to be of congenital origin; in others, drugs, such as the sulfanilamide derivatives, and also pyelonephritis have been implicated. The defect is not localized to the distal tubule in all cases because hyperphosphaturia and hypophosphatemia have been observed [*48*]. The association of this disorder with the full-blown form of Lignac-Fanconi's syndrome has already been mentioned.

The clinical picture varies with age of onset, severity of the defect and nature of the chemical losses. Such patients usually suffer from excessive thirst and polyuria. If the serum potassium reaches low levels, muscular weakness and even paralysis may appear. As a result of the alkaline urine and hypercalcinuria, nephrolithiasis and nephrocalcinosis are often seen. Progressive renal insufficiency may develop in such patients and they die in uremia.

The skeleton suffers in two ways: (1) as a result of the chronic acidosis, calcium is mobilized directly from the bones and this is associated with the development of osteitis fibrosa, and (2) in other cases in which the loss of calcium and phosphate in the urine is excessive, rickets or osteomalacia may be in the foreground. Frequently, there is an overlapping of these two bone diseases.

For the treatment of this disorder various alkalinizing mixtures have been advocated. Shohl's regimen containing a mixture of citric acid and sodium citrate has been the most popular [*49*]. These substances are easily absorbed and well tolerated. The citrate moiety is readily metabolized, adding sodium directly to the depleted pool of fixed base. This results in an elevation of the bicarbonate concentration of the plasma. The additional fixed base presented to the kidney reduces the negative cation balance and specifically curtails calcium loss. The additional administration of a few grams of calcium gluconate daily is helpful. Administration of basic sodium phosphate has also been recommended [*50*].

Saville et al. [*51*] emphasize the dangers of hypokalemia in this condition. This is often intensified by the administration of sodium salts. To combat this complication they recommend the use of tablets containing one part of potassium bicarbonate and three parts of sodium bicarbonate. Another efficacious form of therapy consists of the use of a mixture containing 140 mg. of citric acid, 75 gm. of sodium citrate and 25 gm. of potassium citrate dissolved in 1 L. of water. One ounce of this mixture is given three to five times daily [*41*].

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Clinico-pathologic Conference

Surgical Hypophysectomy for Diabetic Retinopathy

STENOGRAPHIC reports, edited by Lillian Recant, M.D., and W. Stanley Hartroft, M.D., of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THIS twenty-nine year old white male tool inspector was admitted to Barnes Hospital for the first time on August 23, 1956. He died on October 30, 1956. His chief complaint was decreasing vision for two years.

At the age of five diabetes mellitus developed for which he received insulin. Little is known about his early illness, but from the age of fifteen he had taken 45 to 50 units of protamine zinc insulin every morning without following any diet or regular meal hours. During this period he experienced many insulin reactions during the day which were characterized by numbness of the hands and feet, sweating, headaches and difficulty with mental processes. These episodes were relieved by carbohydrate taken orally. He also had nocturnal convulsions associated with sweating which were apparently relieved by his wife's pouring orange juice into his mouth. Four years before this admission an ulcer developed over the left ankle which healed quite slowly. At about that time the patient stated that acidosis developed and he went into coma for ten days despite therapy at another hospital. After that he was started on a strict diet which was soon discontinued because of increased insulin reactions.

Two years before this admission the patient noted red spots interferring with the vision of his left eye. Gradually the vision of the left eye decreased to bare light perception. The right eye had been free of visual disturbance until one month before admission when red spots developed on that side. He denied recent polydypsia or polyuria. He had been taking protamine zinc insulin, 48 units daily, for several weeks prior to admission. His urine sugar was usually low in the morning and 4+ in the evening. In addition, history was obtained of frequent skin infections for many years. For one and a half years before this admission he had suffered from nocturnal cramping and burning and occasional paraesthesias in the extremities. He was unable to distinguish between hot and cold on his lower legs.

The patient was adopted and did not know his family history. In 1945 he fell fracturing his right wrist and second, third and fourth cervical vertebrae. Convalescence was uneventful. The review of systems was non-contributory.

The physical examination on admission revealed the following: temperature, 37°C.; pulse, 96; respirations, 18; blood pressure, 125/80 mm. Hg. The patient was well developed and well nourished. There were many scars of old infections covering the arms and legs. Only gross light perception was present in the left eye; fairly good vision was maintained in the right eye. Old and new vitreous hemorrhages obscured the retina in the left eye. There was marked retinopathy in the right eye with retinal hemorrhages, capillary aneurysms and newly formed capillaries. There was marked retinitis proliferans at the disc with arching forward into the vitreous. Examination of the ears, nose and throat was within normal limits. The thyroid was not abnormal. The chest was clear. The heart was not enlarged. There was normal sinus rhythm and no murmurs were heard. No abdominal organs or masses were palpable. The rectal sphincter tone was described as poor. The dorsalis pedis pulses were markedly decreased bilaterally. There was a proximal sensory gradient in both legs. Temperature sensation was lost below the ankles and proprioception was decreased in both feet. The achilles sensation test was positive. Ankle jerks were absent.

Laboratory data on admission disclosed the following: hemoglobin, 14.6 gm./100 ml.; white blood cells, 7,500/cu. mm. with the following differential leucocytic pattern: bands, 1 per cent; polymorphonuclear leucocytes, 69 per cent; lymphocytes, 29 per cent; monocytes, 1 per cent. The red blood cells and platelets appeared normal on stained film of the blood. Urinalysis disclosed a specific gravity of 1.032. The pH was 6. There was 4+ glycosuria but no proteinuria. A rare white blood cell was seen in the centrifuged sediment. Stool was guaiac negative. The cardiolipin test was negative. Fasting blood sugar was 43 mg./100 ml. (without symptoms). Blood chemical analyses disclosed the non-protein nitrogen to be 17 mg./100 ml.; cholesterol, 151 mg./100 ml. Phenolsulfonephthalein excretion was 35 per cent in 15 minutes. Lumbar puncture was performed revealing crystal clear fluid with an initial pressure of 160 mm. Two cells were seen without acid; the protein was 85 mg./100 ml.; the sugar, 168 mg./100 ml.; the Wassermann test was negative and colloidal gold was 0000000000. A repeat lumbar puncture on August 29 disclosed normal manometrics. Roentgenographic examination of the chest was within normal limits.

The patient was started on a 2,500 calorie diet consisting of: protein, 70 gm.; carbohydrate, 250 gm.; and fat, 135 gm. He was given 40 units of NPH insulin every morning. Regulation proved difficult. Urinary glucose spill was heavy and unpredictable. At times he excreted as much as 100 gm. of glucose a day. Decreasing the insulin dosage to rule out rebound hyperglycemia increased the glycosuria. Closer regulation was obtained with the administration of 40 units of NPH insulin before breakfast and 20 units before lunch. After several days of decreased glycosuria he had a grand mal seizure at 10 p.m. which was thought to be secondary to hypoglycemia. The dose was lowered to 35 units of NPH insulin administered before breakfast and 15 units before supper, but three days later, on September 12, the fasting blood sugar was 48 mg./100 ml. On September 18 at 4:30 p.m. the patient had another clonic seizure after taking 35 units of NPH insulin that morning.

The decision was made to perform a hypophysectomy in an attempt to slow down or halt the progression of his retinopathy. On September 19, the operation was performed. The patient had received 100 mg. of cortisone intramuscularly on the night before the operation and again on the morning of the operation. During the surgical procedure, a continuous intravenous drip of 10 per cent glucose in water with 100 ml. of hydrocortisone per liter was administered. A craniotomy was performed via left frontal incision. The anterior pole of the left frontal lobe was amputated. Because of a short falx and conjoined anterior hemispheres, the right frontal lobe was also entered. After some difficulty because of this fusion the sella was reached. The pituitary stalk was clipped and the gland removed. It was believed that complete pituitary removal had been obtained.

Immediately postoperatively the patient did well. He was given 50 mg. of cortisone intramuscularly every six hours. Continuous infusions of 5 per cent glucose in water were maintained. The purpose was to assure some glycosuria while maintaining the urine free of acetone. Small doses of regular insulin were administered and loss of urinary glucose was followed closely. Urine volume was also measured every two hours and pitressin® was administered when it became excessive. The plasma electrolytes remained quite stable. On the first postoperative day the patient received a total of 32 units of regular insulin. By the second postoperative day he was taking small amounts of fluid orally. His blood sugar was 204 mg./100 ml. His urine sugar remained 4+. On the fifth postoperative day he was started on 15 units of NPH insulin and 5 units of regular insulin before breakfast. On the sixth postoperative day, the patient was unresponsive. Blood sugar was 126 mg./100 ml. He seemed to respond slowly to intravenous glucose. Blood sugar that morning had been 172 mg./100 ml. Dilantin® 0.1 gm. was administered three times daily throughout the postoperative period.

On the tenth postoperative day the patient was transferred to the medical service. At that time he was receiving 17 units of NPH insulin and 5 units of regular insulin every morning. His cortisone dosage had been decreased to 25 mg. every six hours. His urine sugar was approximately 10 gm./day; however, the fasting blood sugar varied from 375 to 510 mg./100 ml. On the eleventh hospital day, five minutes after receiving pitressin tannate in oil, the patient became obtunded and moderately hypotensive with his blood pressure approximately 90/70 mm. Hg. Fifteen minutes later his fasting blood sugar was 375 mg./100 ml. An electrocardiogram showed ST elevation with T-wave inversion in leads V2 through V4. This change was

interpreted as suggestive of subepicardial myocardial injury. The patient was oliguric for five to six hours but then began to urinate as before. An electrocardiogram taken on the next day showed normal complexes in V2 through V6. Roentgenograms of the chest were negative for pulmonary infarction. On the fifteenth postoperative day, because of clumped white cells in the urine, a urine culture was obtained which grew out coliform bacilli. The patient was treated with gantrisin.® He was ambulated on the sixteenth postoperative day and his serum CO_2 which had been slightly elevated since operation reached 38.9 mEq./L. Urine was persistently alkaline, possibly because of the potassium triplex which he received in the dosage of 4 ml. three times a day. He displayed little interest in what was going on. He was lethargic and docile.

On the twentieth postoperative day after receiving his usual morning insulin (12 units of NPH insulin and 5 units of regular insulin) he had three insulin reactions, one with a convulsion. His blood sugar was reported as 14 mg./100 ml. His cortisone dosage on that day totaled 50 mg. He became somewhat hypotensive in the range of 100–90/70–60 mm. Hg for eighteen hours. There was no change in his heart rate. His temperature dropped to 34.9°C. His final maintenance therapy consisted of cortisone, 12.5 mg. three times daily; thyroid, 60 mg. daily; testosterone propionate, 10 mg. daily, and pitressin tannate in oil, 1 ml. as necessary to control polyuria. On the twenty-third postoperative day, administration of potassium triplex was discontinued. Potassium chloride from 1.5 to 3 gm. per day was substituted. A week later his urine pH was 5.5. Subsequently his carbon dioxide varied between 28 and 35 mEq./L. His affect continued to be flat. He had episodes of subnormal temperature and mild hypotension which were not known to be associated with hypoglycemia.

After the twenty-fifth to twenty-sixth postoperative day the patient suffered from rather constant anorexia and nausea. It was difficult to get him to take his medications. His lethargy waxed and waned, but steadily progressed. The pus cells had disappeared from the urine after the use of gantrisin but subsequently recurred. Proteus and mixed proteus and coliform organisms were cultured from the urine. On the thirty-third postoperative day, administration of achromycin® was begun.

On approximately the thirty-fifth postoperative day he began having episodes of vomiting. Fluoroscopic examination of the gastrointestinal tract revealed no cause for his gastrointestinal complaints. The insulin dosage was gradually decreased to 5 units of NPH insulin and 3 units of regular insulin administered every morning. On the thirty-eighth postoperative day acetonuria appeared. He was spilling only small amounts or no glucose in the urine. An intravenous infusion of 1,000 ml. 5 per cent glucose in water was administered. Despite this extra glucose he had convulsions later in the day. His oral intake remained low. On the thirty-ninth hospital day his temperature rose rapidly to 40.1°C. and he had a shaking chill. He vomited bile-stained material. The urine was abundant with white blood cells. Blood culture failed to grow any organism. Roentgenographic examination of the chest was within normal limits. The spinal fluid contained only 1 cell/cu. ml.; protein was 251 mg./100 ml. Chloramphenicol was administered.

For the remaining two days of his life the patient's temperature remained approximately 39–40°C. His blood pressure became unobtainable and was raised only after massive doses of norepinephrine. The addition of large doses of hydrocortisone, ACTH, aqueous adrenocortical extract and erythromycin did not halt his downhill course. On the day of his death his serum sodium was 135.1 and his potassium was 3.3 mEq./L. Urinalysis disclosed only two to three white blood cells per high power field. Urine culture the day before had grown confluent coliform organisms.

CLINICAL DISCUSSION

DR. CARL V. MOORE: We can review the principal problems in this patient very quickly. He was a white man, twenty-nine years of age, with a history of poorly controlled diabetes since the age of five. He had poor vision in his left eye for two years and failing vision in the right eye for one month. He had a highly technical job, and was the sole support of his family. It was clear to him that he would be unable to handle his work much longer if his sight continued to deteriorate. He had paraesthesias in his legs and many skin infections. He had marked retinopathy. There were vitreous hemorrhages, retinal hemorrhages, capillary aneurysms and retinitis proliferans in the right eye. Dorsalis pedis pulsations were decreased bilaterally. There were

sensory changes in the ankles. He had no sensation in the achilles tendon and ankle jerks were absent. The laboratory data showed that he had glycosuria and elevated spinal fiuid protein but all the rest of the laboratory examinations were essentially normal. It is of importance that all urinary examinations, except for the last two following an infection in the urinary tract, showed no proteinuria. His diabetes was difficult to control. There were wide swings in his blood sugar level. He would spill as much as 100 gm. of glucose a day. There was quite a debate as to whether a therapeutic adrenalectomy or hypophysectomy should be performed. The decision was made to perform the latter. I would like to concentrate somewhat upon this debate. Dr. Becker held the opinion that this patient's retinal changes were so marked that he was a poor case for us to use as the first subject for hypophysectomy or adrenalectomy at this institution. He believed that we would never be able to evaluate the results. Dr. Sherry, I believe, was somewhat opposed to the procedure. Dr. Reichlin thought that he was probably not a good candidate. Dr. Daughaday was somewhat more in favor of surgery since this provided the only possible means of altering the patient's basic problems. Dr. Jan Waldenström was here at the time as visiting professor. He was familiar of course with the extensive experience with hypophysectomy in Sweden and suggested that this patient would be a good candidate. Dr. Schwartz and Dr. King of the neurosurgery service saw the patient. They were not anxious to do the procedure. They explained carefully what was involved to the patient and to his family. The final decision to proceed was a desperation measure to all.

It seems to me that there are no real diagnostic problems involved here except as related to the terminal episode. Our discussion might therefore be centered about eight problems. First of all, what is the physiologic and biochemical relationship of the pituitary and the adrenal to insulin and carbohydrate metabolism? Second, what is the relationship of the pituitary and the adrenal to the vascular lesions in the retina, kidney and elsewhere in diabetes? Third, is there any evidence of disturbed adrenal function in diabetes? Fourth, what are the experiences with adrenalectomy in diabetic patients with retinopathy and nephropathy? Fifth, what are the experiences with hypophysectomy in similar patients? Sixth, how does one manage a patient after hypophysectomy? Seventh, why did terminal hypotension, anorexia, nausea and hypothermia develop and why did our patient die in shock? Eighth, was the terminal episode due to bacterial shock superimposed on hypopituitarism? Was it due to a hypothalmic lesion or to something else? I would like to ask Dr. Recant to begin by reviewing the physiologic and biochemical relationship of the pituitary and the adrenal to carbohydrate metabolism.

DR. LILLIAN RECANT: Our understanding of these relationships stems largely from the work of Houssay and Biassotti in 1929. Houssay demonstrated that severely diabetic pancreatectomized dogs showed a striking amelioration of their diabetes following hypophysectomy. His work was logically followed in the early 1930's by the demonstration that the administration of crude anterior pituitary extract enhanced the diabetes in partially pancreatectomized animals. The next step came in 1937, when Young induced diabetes in an animal with an intact pancreas by the administration of material obtained from the anterior pituitary. Research thereafter was directed first towards the identification of the factors in the pituitary which are responsible for the diabetogenic effects and second towards an investigation of the mechanism of the diabetogenic action.

In order to approach the problem as we see it today, let us start with the position of insulin in the metabolic scheme. What do we know about the action of insulin and in what way can the pituitary or adrenal factors behave as anti-insulin factors? The major effects of insulin are: (1) to increase the uptake and utilization of glucose by tissues and (2) to decrease the hepatic glucose release. The net effect of these processes is to produce a lowering of the blood sugar. Probably as secondary effects of these actions of insulin, decrease in protein breakdown, decrease in gluconeogenesis from protein and enhancement of fat and protein synthesis occur. The exact site or mechanism of action of insulin has not yet been definitely proved. The two theories of insulin action most widely held at the present time are (1) the transport theory and (2) the hexokinase theory. The first suggests that insulin accelerates and facilitates the transport of glucose across the cell membrane, hence providing free glucose as substrate for the intracellular enzymes concerned with utilization of glucose. The second theory suggests that insulin directly affects the activity of the enzyme hexokinase, and in this way accelerates glucose metabolism.

For the purpose of this conference we need not go into any more detailed consideration of these theories. Now, what do we know of the anti-insulin factors which have been obtained from pituitary? Growth hormone has been shown to be one of the most potent diabetogenic materials in the pituitary. This hormone appears to act antagonistically to insulin in that it decreases glucose uptake by tissue and inhibits fat synthesis. Adrenocorticotropic hormone (ACTH), the second hormone from pituitary, acts by increasing adrenal steroid production. The steroids increase protein catabolism and gluconeogenesis. In addition they potentiate the peripheral effect of growth hormone by further inhibiting glucose uptake by muscle. Finally, both growth hormone and ACTH significantly interfere with fat synthesis.

Two other hormones have been shown to be involved to some extent in the diabetogenic activity of pituitary. One is the thyrotropic hormone, but its mechanism of action has not yet been clarified. It is suggested that with increased thyroid activity, more insulin may be degraded and that a relative deficiency of insulin may result by virtue of the enhanced metabolic rate. Prolactin, the lactogenic hormone, has been shown to increase the blood sugar in animals and to act as an anti-insulin factor but no work is yet available to explain the mechanism. The hormonal relationships in human diabetes with regard to insulin and anti-insulin factors are not perfectly defined. However, recent information indicates that diabetic plasma "insulin activity" may vary from essentially no insulin, to levels that are far above the normal. It seems reasonable to assume that in order for diabetes to appear, some imbalance must exist between the insulin level and perhaps the diabetogenic anterior pituitary hormone levels. The normal subject can be depicted as maintaining a balance between insulin and the anterior pituitary hormones. In pancreatic diabetes, one can conceive of an imbalance resulting from an insulin deficiency with a normal level of anterior pituitary factors. In pituitary diabetes, as seen in acromegaly, there may actually be increased "insulin activity" in the plasma, but here the imbalance is most certainly due to greater than normal levels of anterior pituitary factors.

DR. MOORE: I think it is a logical step from where Dr. Recant has taken us, to go to the question of the relationship of the pituitary and the adrenal to the retinal and renal vascular changes in the diabetic patient. Dr. Becker has been intimately associated with this problem but unfortunately he is out of town. Dr. Sherry, would you be good enough to review for us the present status of the evidence indicating that steroids are related to the development of these vascular lesions?

DR. SOL SHERRY: I think we owe to Dr. Becker the observation that one can now experimentally produce diabetic retinopathy in animals. If one injects alloxan diabetic animals with steroid hormones, such as cortisone, diabetic retinopathy with capillary aneurysms can be almost uniformly produced. In addition, studies in some diabetic subjects with retinopathy in contrast to diabetic subjects without retinopathy, seem to show slight but significant increases in urinary steroids. So faced with those two observations, there is considerable suggestive evidence that the adrenal steroids may play an important part in provoking the retinopathy that is seen in diabetes. Some people, however, are still somewhat skeptical of this mechanism.

DR. MOORE: Yes, When I talked to Dr. Becker about attending this conference, he said that he hoped it would be made clear that not everyone was in total agreement with him on the relationship between the steroid hormones and the development of the capillary aneurysms. That brings us to the third question. Dr. Eisenstein, is there any evidence of disturbed adrenal function in diabetes? There are many people who believe that if diabetes is kept under good control, retinopathy does not develop, but if diabetes is poorly controlled, then one can expect vascular lesions of a severe degree. There are those who believe that the patient whose blood sugar undergoes wide fluctuations is subject to similar fluctuations in adrenal cortical activity. Now if all these things are true, that is if increased adrenal activity does cause vascular lesions, if poor control of diabetes is related to vascular lesions, and if poor control causes an increased output of steroids, then this patient's adrenal cortical activity may have been closely related to the development of progressive blindness. Would you review for us in addition to the material Dr. Sherry has already mentioned, the evidence that there might be increased steroid activity in patients with diabetes?

DR. ALBERT EISENSTEIN: Dr. Moore, the first thing one ought to dispose of when discussing the urinary excretion or blood level of adrenal steroid hormones in diabetic patients is those pa-

tients who have diabetic acidosis or are in coma. It has been conclusively demonstrated through the work of McArthur, that there is in diabetic acidosis a greatly increased quantity of circulating adrenal steroid hormones. Now what is the situation in diabetic subjects who are not acidotic or in coma but are living an active life? There is evidence which indicates that there may be increased adrenal function in certain of these subjects. First, it has been shown that when response to ACTH is measured using the eosinophile count, persons who have the complications of diabetes, particularly retinopathy, show evidence of increased adrenocortical hormone secretion. Secondly, Dr. Becker and his group made a limited number of observations concerning the urinary excretion of adrenal steroid hormones in diabetic subjects. Their conclusion was that in subjects with complications of diabetes larger quantities of adrenal steroid hormones were excreted than in diabetic subjects without complications. Thirdly, it has been found in postmortem studies that adrenal weights are somewhat greater in diabetic subjects with complications than in those without. I believe an increased incidence of adenomas of the adrenal gland was also found in this group.

One of the best studies concerning adrenal function in diabetes is the one of Klein. These investigators studied a relatively large number of juvenile diabetic subjects. They compared adrenal function of these juvenile diabetic children with that of a group of normal children with minor illnesses of a non-metabolic nature and also with that of a group of institutionalized children. They observed that in their group of juvenile diabetic subjects, there was evidence of an increased level of circulating adrenal cortical hormones as compared to the two control groups. Of even greater interest, was the fact that they found that they could divide their juvenile diabetic subjects into two groups. One group with poor control demonstrated an increased number of complications, while the other group seemed to be under better control and demonstrated fewer complications. They noted that when they compared the blood concentrations of adrenal cortical hormones of these two groups that the group with complications demonstrated higher levels than did those diabetic children who were under better control.

To summarize, there is a moderate amount of information which would suggest that increased adrenal cortical function occurs in diabetes and, particularly, in those patients with complications. However, not all investigators agree with this. One of the junior medical students, Robert Lindemeyer, working in my laboratory studied this specific problem. Although we have only a limited number of observations, we were unable to find any evidence of a correlation between adrenal cortical activity as represented by the excretion of hormones in urine and the incidence of complications of diabetes. I do not think that the question can be completely answered at this time.

DR. MOORE: Dr. Reichlin, since there is at least a question about increased activity of the adrenal cortex, this leads us to consider the fourth of my subjects here, namely the therapeutic approach with bilateral total adrenalectomy. Would you be good enough to tell us what the experiences have been with that operation?

DR. SEYMOUR REICHLIN: The possible usefulness of the operation of total adrenalectomy is certainly suggested by the observations that Dr. Becker and others have made. It has also been incidently noted that in diabetic patients who had adrenalectomy primarily for essential hypertension there was improvement in the vascular disease. There are several small series in the literature, of patients who were subjected to total adrenalectomy for diabetes, as well as several isolated case reports. One series of seven cases was reported by Wortham and Headstream in 1954. The patients were diabetic with progressive renal failure, and adrenalectomy was performed as a measure of desperation. Dr. Wortham observed that in most of the patients there was either improvement or no further deterioration in their visual status. As a matter of fact, on the basis of this observation we were prepared several months ago to perform bilateral adrenalectomy on a patient smilar to the one presented here today. I called Dr. Headstream to find out what his latest experience had been. He told me that although the visual status had often improved, not one of his seven original patients was alive two years after the operation. In his series, total adrenalectomy did not prevent the progression of the diabetic vascular complications in the kidney. As a matter of fact, although there were some cases in which albuminuria was reduced initially, after five to eight months albuminuria ultimately grew worse. Another series of six cases was recently reported in *Lancet* by Malins. Retinopathy was improved or unchanged in four cases but there

was one patient who had a vitreous hemorrhage two months after adrenalectomy. In these patients there was no change in renal status. It appears that at present there is no good evidence that the procedure affords much benefit in the treatment of the vascular complications of diabetes.

DR. MOORE: Dr. Daughaday, would you review for us what the experience has been with hypophysectomy as a therapeutic approach?

DR. WILLIAM DAUGHADAY: Perhaps I could say to begin, that I do not believe the adrenal steroids are the most important etiologic factor in the causation of diabetic retinopathy. They probably have an aggravating effect but to me the evidence that they are the major cause is most unsatisfactory. I have been more inclined to look to the pituitary, which is unknown ground as far as many of its functions are concerned. Further, I have been intrigued by the results that have been obtained by hypophysectomy in the hands of Luft and Olivecrona in Sweden. The number of patients who have been operated on is rather few. The largest series that has been published in detail by these authors is twenty patients. In one series of nineteen patients, they had a total of seven deaths in the immediate postoperative period and the following four to six weeks. Of the twelve patients who survived these operations, there was only one patient in whom the diabetic retinopathy progressed. Considerable subjective improvement in vision was recorded in several patients while two patients objectively improved. Luft and Olivecrona have been somewhat conservative in their official interpretations of these results. We have to realize that we are dealing with a process which can be likened in many respects to cancer in that a poor prognosis exists and drastic procedures are justified. The second rather extensive series of hypophysectomies collected by Gordon at the University of Wisconsin was reported at the Central Society in November, 1956. At that time eleven patients were reported on. Only one of them died an operative death while two of them died after they left the hospital, presumably of hypoglycemia. The remaining eight showed "striking improvement" in the retinopathy. Gordon further states, "Several had measurable return of vision." This seems a little inconsistent. However, I talked with Dr. Gordon and he has retinal photographs showing that apparently the retinal process was arrested in many of these patients. Kinsell had four patients, two of whom died at operation, and one in whom hypophysectomy was incomplete, so he ended up with one patient who could not be evaluated. There is reason to justify this therapeutic approach to diabetic retinopathy since we lack anything better, but results certainly cannot be called conclusive.

DR. MOORE: We now come to the post-operative period which was unfortunate and very difficult for the house staff.

DR. EISENSTEIN: Before we go on any further in the discussion, Dr. Moore, there is one very important point that should be made concerning retinopathy. Diabetic retinopathy may wax and wane, particularly early in the course of development. It is not always true that once retinopathy is present there will be steady progression until the person has total loss of vision. Actually, in the early cases, there may be more capillary aneurysms and hemorrhages at one time and fewer somewhat later in the patient's course. It might also be said that even in patients who have fairly advanced retinopathy, there may occasionally be a slowing down or halting of the process.

DR. MOORE: Yes, that deserves emphasis. The people who have written about their results with hypophysectomy have pointed out how difficult it is for them, therefore, to be able to evaluate their results. Dr. Daughaday, would you comment on the management of a patient after hypophysectomy. Do you in retrospect have any criticism of the way in which this patient was handled?

DR. DAUGHADAY: The first statement that deserves emphasis is the fact that the postoperative course of hypophysectomy in diabetes is much more severe than that following hypophysectomy in cancer. The reason for this is not entirely apparent except that one of the indications for hypophysectomy in the diabetic patient is severe vascular disease and this process exists in the smaller vessels of the brain. Minor pressure exerted on the brain, which is tolerated very well in non-diabetic subjects, seems to lead to cerebral edema and hemorrhages that can greatly complicate the course in the diabetic subject. In any hands, the operative mortality in these diabetic subjects may be three to five times greater than in patients with carcinoma. With that in mind, the maintenance of patients following hypophysectomy requires the careful regulation of fluid and electrolyte balance and the prevention of adrenal insuffi-

ciency. To prevent hypoadrenalcorticism, cortisone in doses from 100 to 300 mg. a day may be used for the day preceding operation and during the immediate postoperative period. In the presence of hypotension, intravenous hydrocortisone and norepinephrine can be added, Desoxycorticosterone is not usually necessary, since the patient is receiving enough salt retaining effect from cortisone. Olivercrona thinks that desoxycorticosterone may actually be harmful. Replacement of thyroid eventually will be necessary.

DR. MOORE: How soon?

DR. DAUGHADAY: Thyroid is usually not given until the initial difficulties have been passed. You all must be aware that acute, temporary or even permanent diabetes insipidus is a common problem in hypophysectomy. This patient had a mild diabetes insipidus that required pitressin tannate. Usually pitressin is given in aqueous solutions at first and later in oil as the patient becomes stabilized.

DR. MOORE: Should one also include testosterone?

DR. DAUGHADAY: I have been concentrating mainly on the initial postoperative course, but in the maintenance therapy, I believe that testosterone in a man, or estrogens in a woman, have a great deal to do with restoring the feeling of well-being. We do not know exactly which hormones are responsible for either the good or the bad effects of hypophysectomy so that the tendency has been to try to maintain these patients symptom-free on the lowest possible dose of cortisone and other hormones.

DR. MOORE: Unfortunately Dr. King who performed the operation is out of town. Since Dr. Schwartz is not here either, would you Dr. Kerr care to comment?

DR. FRED KERR: As you know, this is the first hypophysectomy for diabetes performed at this hospital and so consequently most of what I will say or can say is going to be on the basis of what I have read in the literature. The point I think is of some interest is that electrolyte imbalance is not much of a problem. I would like Dr. Daughaday to confirm this, if possible. It is not as serious a problem as was originally believed because the adrenal apparently can do fairly well in maintaining the electrolytes since aldosterone secretion is apparently not influenced to any extensive degree by hypophysectomy. Furthermore, with the maintenance dosages of cortisone, this problem seems to be fairly well handled. The main problems as far as the postoperative situations are concerned are the ones that Dr. Daughaday mentioned with regard to cerebral edema. It has been found helpful to resect a portion of the frontal lobe for exposure. The cerebral edema is frequently compensated by this type of internal decompression. In this patient, there was a certain amount of difficulty in resecting this medial aspect of the frontal lobe and perhaps that led later on to the complications, particularly the mental state and the somewhat unfortunate postoperative course. Dr. King had some difficulty in separating the two frontal lobes as they were adherent and since this area is to a certain extent involved in the processes of consciousness, some complications were not unexpected. The other problem that comes up is the matter of whether or not a total hypophysectomy can be obtained. The possibility of regeneration of the portal venous system in the stalk of the hypophysis with the return of function of the hypophysis at a later date must be considered.

DR. DAUGHADAY: One of the peculiarities in diabetic subjects following hypophysectomy is the great tendency for convulsions to develop. That was a very real problem in this patient. Some convulsions respond to glucose and high doses of cortisone. Others do not. Some of them have been associated with hypoglycemia and others have not.

DR. MOORE: We are now into the seventh and I guess the final problem that will be covered here. What caused the patient's lethargy, his convulsions and other complications? Dr. Daughaday has already pointed out that some of these convulsions responded to glucose. One alert house officer checked the patient's blood sugar during or immediately following the convulsion on October 2. He found that the blood sugar level was 345 mg. per cent. Dr. Recant, can you have a hypoglycemic convulsion in the face of hyperglycemia?

DR. RECANT: It would be incorrect I suppose, to call this a hypoglycemic convulsion in the face of a normal blood sugar value. However, those who have followed diabetic subjects, particularly juvenile diabetic subjects, have observed that these patients appear to have the classical symptoms of hypoglycemia as the blood sugar is rapidly falling, although the measured value of blood sugar may be within normal limits. I have discussed this problem with Dr. O'Leary and Dr. Hartman and they are convinced that this

occurs, although the explanation is not clear. It certainly seems that prolonged and recurrent hypoglycemic episodes can produce cerebral damage. Further the question arises as to whether or not the threshold for convulsions in a patient with brain damage is not somewhat reduced so that at normal blood sugar levels these patients may be susceptible to convulsive episodes. I suspect that such may be the case and that perhaps in these people, in order to achieve saturation of the enzymes in the brain with glucose, a higher than normal blood sugar level is required. I think the evidence is non-existent at the present time but this is a possible explanation.

DR. MOORE: Dr. Daughaday, one final question in two parts. Since our patient did not have severe diabetes insipidus, must we assume that the hypophysectomy was incomplete? Can you tell us why you think he did so poorly and went into hypothermia and shock?

DR. DAUGHADAY: The first question is quite simple because the antidiuretic hormone is not released solely by the posterior pituitary but is released by the entire neural hypophysis which includes the stalk and the median eminence. Probably although the patient had some inadequacy of this system, he had some residual pitressin releasing tissue left behind. That does not indicate incomplete hypophysectomy however.

The reasons why this patient did so poorly, are multiple. One factor was his depressed psychologic attitude, which existed to some extent before operation and made postoperative care difficult. The operation was complicated and inadvertently a considerable amount of damage was done to both the frontal lobes and the hypothalmus. This may not be easily demonstrable pathologically, but I interpret the hypothermia, the difficulty in maintaining blood pressure and the increased defect in affect, as being related to brain damage. He had other problems such as infection and problems in potassium regulation which were secondary.

DR. MOORE: The last thing I was going to ask was whether or not bacterial shock was the terminal episode. I think we have to remember that in this patient an infection did develop. He may have had shock on that basis or the terminal high fever might possibly have been on the basis of hypothalamic damage. I do not believe any further summary is necessary; the gross findings will be presented by Dr. Edwards.

PATHOLOGIC DISCUSSION

DR. DAVID EDWARDS: An early, decubitus ulcer was found over the sacrum and multiple, pigmented scars were present on the lower extremities of this slightly wasted white man. The lungs weighed 920 gm. and the larynx and trachea were covered by a yellow, shaggy, adherent membrane which extended into all the branches of bronchi and bronchioles. The lungs were moist and red on cut section and contained multiple, yellow-white, granular patches in the parenchyma. There was marked arteriosclerosis with narrowing of the lumen of the coronary arteries. Minimal arteriosclerosis was present in the other arteries of the body. The pancreas was small and the lobules were distinct. The kidneys weighed 130 and 140 gm. and the capsules stripped with ease from their smooth cortical surfaces. A surgical defect was present in the left frontal lobe. Focal areas of infarction were observed in the medial and inferior aspect of the right and left frontal lobes and a larger infarct, 2 by 3 cm., was present in the white matter of the right frontal lobe. Recent infarcts were also noted in the genu of the corpus callosum, the tips of the caudate nuclei and around the base of the pituitary stalk. The pituitary fossa contained a rim of residual pituitary which measured 3 mm. in thickness. The adrenals were decreased in size and weighed 12.5 gm. An acute, superficial ulcer was present in the pylorus of the stomach.

DR. PAUL E. LACY: Microscopically, the islets of Langerhans appeared to be decreased in number in the pancreas of this juvenile diabetic patient. The sections of pancreas were stained with aldehyde fuchsin in order to determine the degree of granulation of the beta cells. The beta cells were found to be almost completely degranulated. (Fig. 1.) Hartroft and Wrenshall [1] have demonstrated that the degree of granulation of the beta cells and the number of islets can be correlated directly with the insulin content of the pancreas. Since there was marked degranulation of the beta cells and the number of islet cells appeared to be decreased, we can assume that the amount of extractable insulin would be decreased in this pancreas. A slight,

[1] HARTROFT, W. S. and WRENSHALL, G. A. Correlation of beta-cell granulation with extractable insulin of the pancreas. *Diabetes*, 4: 1, 1955.

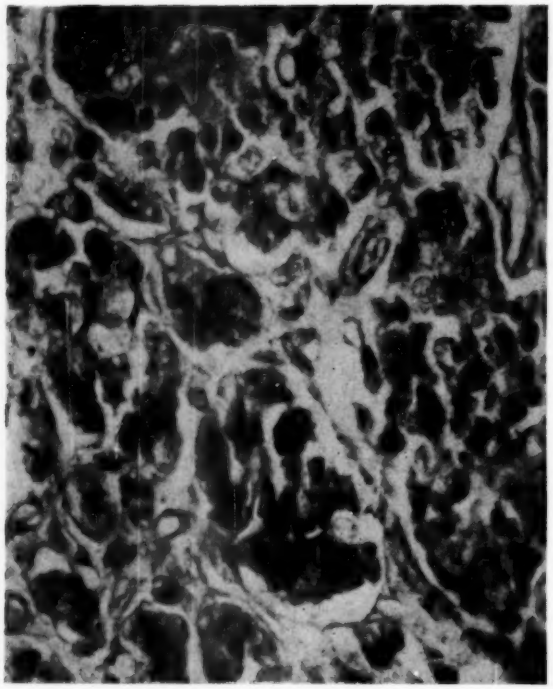

FIG. 1. Portions of two islets of Langerhans showing almost complete degranulation of the beta cells. Aldehyde fuchsin and light green. Magnification, approximately × 340.

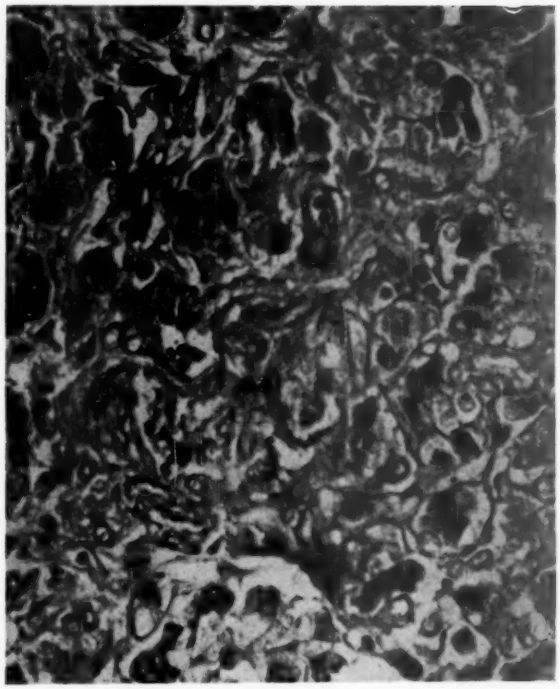

FIG. 2. A focal area of fibrosis of the pancreas is illustrated. Aldehyde fuchsin and light green. Magnification, approximately × 240.

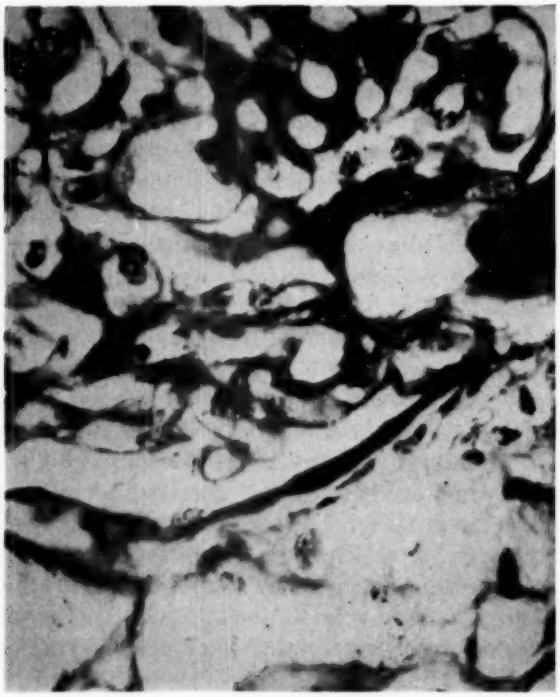

FIG. 3. Marked hyalinization of an arteriole and slight, diffuse thickening of the basement membranes are illustrated. Periodic acid-Schiff stain. Magnification, approximately × 340.

FIG. 4. Electronmicrograph of part of a glomerular capillary loop showing thickening of basement membrane. Red blood cells appear as dense opaque objects in the capillary. The foot-like processes of the podocytes attached to the outer portion of the basement membrane are still preserved. Magnification, approximately × 15,000.

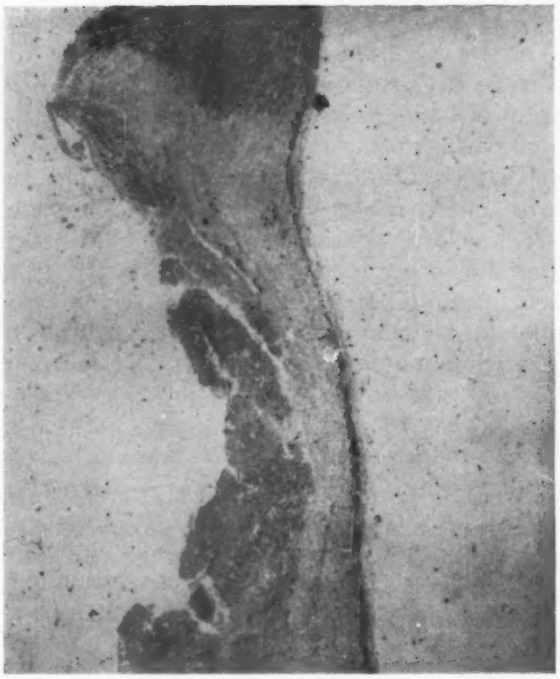

FIG. 5. Section through the remnant of the anterior lobe of the pituitary showing an inner zone of necrotic debris, a mid-zone of ischemic necrosis and an outer zone of normal cells of the anterior lobe. Hematoxylin and eosin.

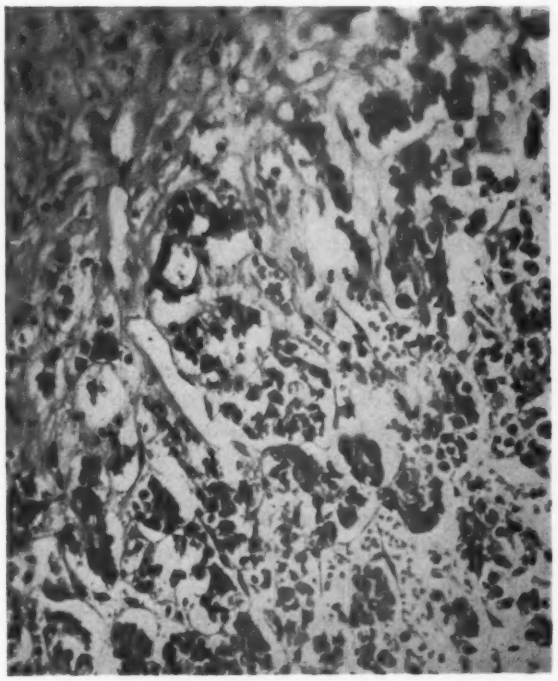

FIG. 6. Junction between the area of ischemic necrosis and the normal-appearing cells in the remnant of the anterior lobe of the pituitary. Hematoxylin and eosin; magnification, approximately × 100.

diffuse fibrosis was present in the pancreas. In some areas, this fibrosis was focal. (Fig. 2.)

The arterioles of the kidneys were hyalinized and thickened. A slight, diffuse thickening of the basement membranes of the glomeruli was present (Fig. 3) but there were no distinct nodular lesions of intercapillary glomerulosclerosis observed in the glomeruli. A small portion of the kidney was removed at autopsy and prepared for examination in the electron microscope. The reasons for this procedure were to determine whether or not enough cytological detail would be preserved to permit identification of the normal structures of the kidney and to determine whether or not it would be possible to study basement membranes of capillaries with the electron microscope. Figure 4 is an electronmicrograph of a portion of a capillary loop in a glomerulus of this kidney. The thickness of the basement membrane was approximately 5,000 Å which is approximately twice the normal thickness. The podocytes of the glomeruli could be recognized and the foot-like processes of these cells were still preserved and were attached to the outer portion of the basement membranes. (Fig. 4.)

A section through the entire remnant of the

FIG. 7. Necrotic membrane replacing the mucous membrane of a bronchus with a diffuse infiltration of neutrophils is illustrated. Hematoxylin and eosin; magnification, approximately × 40.

anterior pituitary is illustrated in Figure 5. There was an inner zone of fibrin and necrotic debris, a mid-zone of ischemic necrosis and an outer zone of normal cells of the anterior pituitary. The junction between the area of ischemic necrosis and the viable cells of the anterior pituitary is illustrated in Figure 6.

The weight of the adrenal glands was decreased and microscopically there was a loss of lipid from the outer portion of the zona fasciculata.

A severe, necrotizing tracheobronchitis was present in the lung. The mucosa was necrotic and the walls of the trachea and bronchi were infiltrated with neutrophils. (Fig. 7.) Multiple foci of bronchopneumonia were present in the parenchyma of the lung. The necrotizing tracheobronchitis and bronchopneumonia were the immediate cause of death.

Microscopic examination of the eyes was done by Dr. Sanders. Vascular retinopathy consistent with but not pathognomonic of diabetes was found. The retinopathy was of long standing and appeared to be subsiding. Retinitis proliferans was present in both eyes but it was more severe in the left eye. Old vitreous hemorrhages were found in the left eye.

Final anatomic diagnoses: Primary: (History of diabetes mellitus, juvenile type; twenty-four years); degranulation of the beta cells and the islets of Langerhans; scars of the lower extremities (history of repeated dermal ulcerations); healed crescentic left frontal surgical incision with underlying bone flap. (History of hypophysectomy for uncontrolled diabetes mellitus, forty-one days); surgical absence of a portion of the left frontal lobe; surgical absence of the neurohypophysis and of the posterior half of the adenohypophysis; atrophy of the adrenals, thyroid and testes, slight; arteriosclerosis of the coronary arteries, advanced; and of the aorta, slight; necrotizing, membranous laryngotracheobronchitis (Micrococcus pyogenes var. aureus cultured at postmortem from the lung, bronchus and blood); bronchopneumonia of both lungs; edema of the lungs; congestion of the lungs; patchy atelectasis of the lungs; acute cystitis; acute peptic ulcer of the pylorus; ischemia of the spleen; thickening of the basement membranes of the glomeruli; decubitus ulcer of the sacrum; needle puncture marks of the antecubital fossae and of the midlumbar area. Accessory: Cyst of the left lobe of the thyroid; focal fat nodules in liver.

Research Society Abstracts

Southern Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE ELEVENTH ANNUAL MEETING, NEW ORLEANS, LOUISIANA, JANUARY 26, 1957

EXPERIMENTAL NYLON AORTIC GRAFTS—LATE RESULTS. *William O. Barnett.* Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

Immediate and early results following the implantation of plastic aortic substitutes have on the whole been satisfactory. Long term follow-ups with late results must be carried out before final evaluation of these materials can be established.

Tubes constructed from nylon filter fabric with a diameter of .8 cm. and measuring 5 to 6 cm. in length were implanted into the abdominal aortas of fifteen dogs. These animals have been studied by means of aortograms, gross photographs and photomicrographs of the various segments of the graft. The oldest dog in this group has had a nylon aorta for twenty-four months. One dog died from distemper after having a graft for four months and the second mortality resulted from disruption of the proximal suture line caused by technical error. Three dogs were sacrificed at various intervals for examination and study. All the other dogs are apparently normal and have bounding femoral pulses. Photomicrographs made after an implantation period of six months or more show the tubes to have been incorporated in a fibrous sheath lined by normal appearing endothelium. There is no incident of thrombosis or rupture in long term survivors.

A STUDY OF THE ACID MUCOPOLYSACCHARIDES OF BOVINE AORTA. *Gerald S. Berenson.* Dept. of Medicine, Louisiana State Univ. School of Medicine, New Orleans, La.

The experiments involve isolation and characterization of acid mucopolysaccharides from bovine aorta obtained from a local abattoir. A crude mixture of mucopolysaccharides was isolated from acetone-defatted aortas. This mixture was resolved by electrophoresis into two fractions with mobilities resembling chondroitin sulfuric acid and hyaluronic acid, occurring with a ratio of approximately 3:1. The electrophoretically uniform, sulfated material was fractionated further into two components, with a ratio of approximately 4:1, by a column chromatograph technic developed for this purpose.

The isolation and characterization of components of ground substance of aorta are of considerable interest. Histochemical studies by several workers suggest an accumulation of mucopolysaccharides in early atheromatous lesions of the aorta. Other experiments indicate that one of the mucopolysaccharides isolated is a potent anticoagulant. Continuation of studies along biochemical lines may lead to a more complete understanding of the nature of disease processes involving cardiovascular structures.

THE CLINICAL AND HISTOLOGIC SPECTRUM OF THE NEPHROTIC SYNDROME. *Leonard B. Berman and George E. Schreiner.* Dept. of Medicine and the Renal Laboratory, Georgetown Univ. Hospital, Washington, D. C.

For the present study we have selected forty-nine nephrotic patients who were personally observed over a six year period. Percutaneous renal biopsy was performed in thirty-six and postmortem examinations in eight. Detailed study of the urinary sediment, quantitative protein excretion, and blood chemistry has been used to establish diagnostic criteria somewhat more satisfactory than those previously used. Correlative data on serum, albumin, cholesterol and calcium have received special emphasis.

The findings of microscopic pathology in forty-four patients suggest a division of this group into eight etiologic categories. These include two which are new to an etiologic classification of the nephrotic syndrome, viz. sickle-cell anemia with miliary infarction, and bacterial interstitial nephritis. The clinical course, response to treatment and prognosis are discussed within the

framework of specific diagnoses. We conclude that specific etiologic diagnosis is now possible in all varieties of the nephrotic syndrome and should precede rational management. Emphasis on specifically diagnosed cases will permit more definite interpretations from correlative data than has previously been possible.

STEROL INHIBITORS OF CHOLESTEROL ABSORPTION. *Maurice M. Best and Charles H. Duncan.* Dept. of Medicine, Univ. of Louisville School of Medicine, Louisville, Ky.

It has previously been reported from this laboratory that β-sitosterol exerts a hypocholesterolemic effect in the cholesterol-fed rat and in man. Recent studies have shown: (1) The inhibition of cholesterol accumulation in serum and liver of the cholesterol-fed rat is greater when sitosterol and cholesterol are fed together than it is when they are fed in separate food pellets (serum and liver cholesterol concentrations of 68 ± 6 mg./100 ml. and 2.7 ± 0.4 mg./gm., respectively, as compared to 97 ± 13 and 11.3 ± 2.9). (2) When sitosteryl palmitate is substituted for the free sterol in equimolar amounts it exerts essentially no inhibitory effect on cholesterol absorption. (3) "Isocholesterol," a mixture of C_{30} compounds derived from wool fat, acts as an inhibitor of cholesterol absorption in the cholesterol-fed rat. The addition of 5 per cent isocholesterol to a 1 per cent cholesterol diet for two weeks resulted in serum and liver cholesterol concentrations of 68 ± 5 mg./100 ml. and 3.4 ± 0.3 mg./gm., respectively, as compared to 82 ± 12 and 12.2 ± 3.9 for the controls.

From these findings it appears that a free hydroxyl group on carbon-3 may be an essential feature of sterol inhibitors of cholesterol absorption. Further, the results support the hypothesis that such substances interfere with cholesterol absorption by tying up the esterification mechanism in some way.

CLINICAL AND PHYSIOLOGIC STUDY OF NORMAL SLEEP AND HYPERSOMNOLENT STATES. *R. I. Birchfield, H. O. Sieker and A. Heyman.* Dept. of Medicine, Duke Univ. School of Medicine, and V. A. Hospital, Durham, N. C.

This investigation was undertaken to elucidate various factors associated with sleep in ten control subjects and in fifteen patients with idiopathic narcolepsy or hypersomnolent disease states, for example, cerebrovascular disease. In addition to clinical observations and psychiatric evaluation, ventilation, arterial blood gases and pH were measured during various stages of sleep monitored by electroencephalography. Narcolepsy was usually associated with moderate obesity or emotional factors and was characterized by frequent daytime napping and disturbances of nocturnal sleep.

With the onset of sleep, the control subjects showed a significant fall in arterial pH (7.39 to 7.34) with elevation of pCO_2 (44 to 49 mm. Hg). These changes were more pronounced in deep sleep but returned to normal immediately on arousal. In narcolepsy there was considerable variation in the awake pCO_2 and pH values without significant change during sleep. Marked alterations in the arterial blood oxygen saturation, pH and pCO_2 occurred primarily during periodic respiration in the hypersomnolent states.

These studies indicate that sleep normally is associated with mild respiratory acidosis. In hypersomnolent states there are no alterations in blood gases or ventilation, e.g. idiopathic narcolepsy, or marked cyclic changes occur due to impaired respiratory regulation as seen in organic disease.

HEPATOJUGULAROMETER, AN APPARATUS FOR QUANTITATIVE CONTROL OF PRESSURE AND FORCE APPLIED OVER HEPATIC AREA FOR HEPATOJUGULAR REFLUX TEST. *G. E. Burch.* Dept. of Medicine, Tulane Univ. School of Medicine, and Charity Hospital of Louisiana at New Orleans, La.

Recent studies of the hepatojugular reflux revealed the need for control of pressure applied over the hepatic area. For this purpose the "*hepatojugularometer*" was devised, an apparatus that consists of a soft flexible rubber bag (basketball bladder), partially inflated with air, to which is attached the mercury or aneroid manometer of the clinical sphygmomanometer. The rubber bag is placed over the hepatic area, and pressure is exerted with both hands upon the bag with a force sufficient to raise the air pressure within the bag to the desired level. Thus it is possible to control and reproduce the force applied over the hepatic area and relate venous pressure quantitatively to it.

Pressure of 50 mm. Hg within the bag was adequate for most purposes. By proper selection of the size of the rubber bag, each mm. Hg pressure is essentially equal to 1 pound of force. Pressure in the median basilic vein of patients with congestive heart failure varied with the

force exerted over the hepatic area, changing relatively little after 50 mm. Hg pressure was reached. Thoracic and abdominal muscular resistance, state of respiration, and other variables must continue to receive consideration in these studies.

ABSORPTION OF TETRACAINE FROM MUCOUS MEMBRANES. *Donovan Campbell.* Dept. of Surgery, Louisiana State Univ. School of Medicine, New Orleans, La.

Reactions from local anesthetics result more frequently from topical application than direct injection into perineural tissue. Tetracaine, one of the most serviceable drugs for topical use, leads in the number of fatalities. It has been assumed but not proved that rapid systemic absorption is the cause. Data on the comparative rates of absorption of tetracaine and circulating blood levels following topical administration and injection into tissue were obtained, using the method of Auerbach, Davis and Foldes in which the drug is coupled with bromthymol blue at a pH of 6 and estimated colorimetrically after extraction from a protein-free filtrate with ethylene dichloride and toluene. In dogs rapid intravenous injection of 4.0 mg./kilo resulted in blood levels of 100 micrograms per cc. in two minutes which dropped to zero within 5 to 6 minutes. Levels of 30 to 40 micrograms in 4 to 6 minutes were obtained following application of the same dose in the pyriform fossa. Identical curves result when the same dose is used as a 2 or 4% solution. Epinephrine 1:100,000 did not retard the absorption. Application to the trachea and bronchi gave higher levels. The same dose infiltrated subcutaneously (0.1%) gave no detectable blood level. The free base resulted in levels similar to those of the hydrochloride. Tetracaine in water-soluble cream gave levels comparable to those of aqueous solutions. Tetracaine in a petrolatum base gave no detectable blood level. These data indicate that tetracaine directly applied to mucous membrane is rapidly absorbed and gives blood levels comparable to a slow intravenous injection.

UTILIZATION OF CREATINE-PHOSPHATE BY MUSCLE EXTRACTS FROM RABBITS WITH NUTRITIONAL MUSCULAR DYSTROPHY. *Mary Carpenter, Paul B. McCay and Ranwel Caputto.* Psychosomatic and Neuromuscular Section of the Oklahoma Medical Research Foundation and the Dept. of Medicine and Biochemistry of the School of Medicine, Univ. of Oklahoma, Oklahoma City, Okla.

Previous investigators have shown that the increased creatinuria of rabbits with diet-induced muscular dystrophy usually precedes any other indication of muscle dysfunction. This observation conflicts with the hypothesis that creatinuria appears when surviving muscle is insufficient to retain creatine. It points to the possibility that the enzyme system which mediates the utilization of creatine-phosphate is particularly susceptible to vitamin E deficiency. Therefore, comparisons were made of the following systems: (1) glycolysis of muscle strips, (2) phosphate transference from creatine-phosphate to hexosephosphates, and (3) the phosphoglucomutase reaction. A group of twenty rabbits was given a modified Mason and Harris diet low in vitamin E. The control group of twenty rabbits received the same diet supplemented by 50 mg. of vitamin E twice a week.

Results show increased glycolysis in the vitamin E-deficient rabbits after twenty-five to forty days on the diet. Thereafter, glycolysis declined and after sixty days was normal or below. In contrast, the transference of phosphate in System 2 declined after twenty-five to thirty days and continued to decrease for the duration of the experiment. In System 3, phosphoglucomutase activity consistently diminished after thirty days in vitamin E-deficient rabbits as compared to the control rabbits. No difference in muscle strength between the two groups was observed until after sixty days.

The data suggest that in vitamin E deficiency, the utilization of creatine-phosphate as well as the activity of other individual glycolytic enzymes may decrease even when the over-all rate of glycolysis is elevated.

IMPROVED METHOD OF MEASURING LOW PLASMA HEMOGLOBIN LEVELS; SOME PRELIMINARY CLINICAL CONSIDERATIONS. *J. V. Cockrell and H. N. Naumann.* Dept. of Surgery and Pathology, V. A. Center, Jackson, Miss., and Univ. of Mississippi School of Medicine, Jackson, Miss.

Measurement of plasma hemoglobin levels in low concentrations by the benzedrine reaction of Wu are not quantitative, as shown by Creditor and confirmed by Crosby and Furth. Unknown inhibitory substances depress the reaction and give erroneously low values. An improved modification for measuring these values is presented which overcomes errors due to inhibition. The principle of our method is performance of the reaction in the presence of the inhibitory sub-

stances by adding plasma containing hemoglobin which has been deactivated by prior addition of H_2O_2. Hemolytic artefacts due to small-bore needles, tourniquet stagnation, vigorous mixing, anticoagulants and centrifugation must be avoided. The method accurately measures heme pigments in plasma in the range of 0.3 to 6.0 mg. per cent, or higher if the plasma is diluted. The upper limit of normal is 2 to 2.5 mg. per cent. Preliminary clinical studies show consistently elevated low-grade levels in sickle-cell anemia, acute pancreatitis, and following many major operative procedures, with and without blood transfusion. Occasional elevations have been encountered in cases of jaundice, pseudomonas meningitis, polycythemia vera and intra-abdominal abscess.

DISTRIBUTION OF ORALLY ADMINISTERED I-131-LABELLED FAT IN THE DOG, WITH PARTICULAR REFERENCE TO CARDIAC AND PULMONARY TISSUE. *B. J. Duffy, Jr. and D. A. Turner.* Dept. of Medicine and Surgery, Georgetown Univ. School of Medicine, Washington, D. C.

I-131-labelled triolein and oleic acid were separately administered to twenty young and four aged mongrel dogs. The animals were sacrificed three hours after ingestion of the labelled fat meal. Tissue I-131-lipid activities were determined by the method of Turner. The per cent concentration of I-131 lipid in the tissues after administration of labelled triolein was found to be eight times that which was observed after administration of oleic acid. The per cent concentration of both I-131 triolein and oleic acid in tissues increased with age in the dog.

There was an average four-fold increase in deposition of I-131-lipid in the heart muscle (left ventricle) compared to skeletal muscle in all animals studied. This initial concentration of orally administered labelled fat in the wall of the left ventricle suggests a probable major role of fat in energy needs of heart muscle. This has been suggested by previous work (Andres) showing the quantitatively minor role of carbohydrate in muscle metabolism.

A sixty-fold increase in the "trapping" of I-131-lipid occurred in the lung of the aged dog compared to that found in the young dog. The greatly enhanced deposition of lipid in the lung of the aged dog may result from a reduced pulmonary capillary bed, deficient plasma dispersal system, or intrinsic change in the lipids deposited. The passage of dietary fat through the pulmonary tissues may be an important step in the normal dispersion of dietary fat in the plasma.

MEASUREMENT OF WORK AND POWER OF HEART BY USE OF LOW-FREQUENCY BALLISTOCARDIOGRAM. *E. E. Eddleman, Jr., William H. Frederick, W. Howard Cooper and Soon Kyu Suh.* Dept. of Medicine, Medical College of Alabama, and Medical Service, V. A. Hospital, Birmingham, Ala.

At the present time there are no easily applicable methods to measure the work and power of the heart in the human patient. Now that linear, oscillatory-free ballistocardiograms can be obtained by low-frequency or aperiodic systems, clinical methods for determining these parameters of heart function have become feasible. If the motion of the ballistocardiographic bed is measured with an accelerometer, the force of each heart beat can be estimated. If the motion is recorded as velocity, formulae for calculating *kinetic energy* or *work* and *power* can be applied. *Work* is proportional to the square of the velocity and *power* to the square of the velocity divided by time. Graphs of both work and power ballistocardiograms will be presented and their relationship to the force traced.

Observations on a group of normal subjects and patients with various types of heart disease, as well as certain animal experiments, suggest that these measurements do indicate heart work and power. However, total work and power cannot be derived as these calculations are based on the momentum trace in one dimension only.

HEMODYNAMIC ALTERATIONS IN PATIENTS WITH ACUTE HYPERTENSION RELATED TO PROXIMITY TO DELIVERY. *Frank A. Finnerty, Jr. and Joachim H. Buchholz and Robert L. Guillaudeu.* Georgetown Univ. Medical Division and Georgetown and George Washington Obstetrical Divisions, District of Columbia General Hospital, Washington, D. C.

Previous studies from this laboratory have shown that acute reduction of arterial pressure with hypotensive agents in twenty patients in an acute hypertensive state (recent rise in arterial pressure, ophthalmoscopic evidence of papilledema and/or flame-shaped hemorrhages and arterial spasm) was accompanied by a 24 per cent average increase in plasma volume and no significant change in red cell mass. A comparable reduction of arterial pressure in patients with chronic hypertension without evidence of recent exacerbation was accompanied by no significant

change in plasma volume. Acute reduction of arterial pressure in twenty-one pregnant or postpartum patients in an *acute* hypertensive state was accompanied by varying responses in plasma volume which were unrelated to changes in cardiac output, mean circulation time or central blood volume. 1. A 33 per cent average reduction in arterial pressure in six patients more than two weeks before or after delivery was accompanied by an average *increase* of plasma volume of 29 ± 8 per cent. 2. A 34 per cent average reduction in arterial pressure in fifteen patients less than two weeks before or after delivery was accompanied by an 11 ± 10 per cent average *decrease* in plasma volume.

The reproducibility of these divergent responses of plasma volume following reduction of arterial pressure in the same patients at different periods of pregnancy suggests that proximity to delivery changes the body's reaction to the acute hypertensive state.

ELECTROLYTE EXCRETION PATTERNS DUE TO CHLOROTHIAZIDE, A NEW ORALLY EFFECTIVE DIURETIC AGENT. *Ralph V. Ford and Charles L. Spurr.* V. A. Hospital, and the Dept. of Medicine and Pharmacology, Baylor Univ. College of Medicine, Houston, Texas.

The electrolyte excretion patterns in ten human subjects given chlorothiazide, 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide have been observed in six fractional periods per twenty-four hours. Six incremental amounts (31.75 mg. to 1000 mg.) as a single dose on two consecutive days were repeated ten times to achieve statistical significance. There was a one- to threefold increased sodium excretion per twenty-four hours, depending upon the dose. The greatest increase (three- to fivefold) appeared in the second two-hour period. Increased potassium excretion paralleled but did not equal sodium excretion. Chloride excretion paralleled sodium excretion, but appeared to be greater after the first six hours, while bicarbonate excretion was most marked and the pH highest during the first six-hour period. Ammonia excretion was depressed during the phase of greatest natriuresis. Titratable acidity increased during the last twelve hours following drug administration and was especially marked during the first post-drug day.

Thus in its initial effects this non-mercurial diuretic agent appears to have properties similar to those of the carbonic anhydrase inhibitors, in its later effects and resembles those of the mercurial diuretic agents. At the doses tested its potency appears to be roughly equal to or greater than orally administered chlormerodrin (neohydrin®).

RELATIONSHIP BETWEEN MOLECULAR SIZE AND TRANSCAPILLARY EXCHANGE IN THE HUMAN FOREARM. *Edward D. Freis, Frank A. Porfido, Harold W. Schnaper and Renato D. Kovach.* Dept. of Medicine, Georgetown Univ. Hospital, and V. A. Hospital, Washington, D. C.

Using methods previously described (*Proc. Soc. Exper. Biol. & Med.*, 92: 188, 1956) for measuring the transcapillary exchange of labeled substances a study was carried out of the relationship between the "permeability" of various substances and their molecular size. The per cent transcapillary losses (means of four or more cases) and effective molecular volumes for four labeled substances were as follows: Rb^{86}, 76 per cent loss, mol. size 11.8 $(A°)^3$ per ion; S^{35}-labeled L-methionine 48 per cent loss, 156 $(A°)^3$ per molecule; S^{35}-labeled glutathione 39 per cent loss, 352 $(A°)^3$ per mol. and I^{131}-labeled diiodotyrosine 29 per cent loss and 278 $(A°)^3$ per mol. These data indicate an approximate correlation with molecular size. The relationship is strengthened by the additional observations that the per cent losses of D_2O at peak concentrations of the dye curve averaged 90 per cent and that inulin (a large molecule) exhibited transcapillary losses averaging 21 per cent.

These data are consistent with the concept of restricted diffusion. The transcapillary losses of substances of small molecular size were too great to be explained on the basis of filtration alone. However, as molecular size increased the trend was toward a progressive decrease in transcapillary exchange.

SERUM LIPOPROTEINS, GLYCOPROTEINS AND LIPIDS IN INSTITUTIONALIZED EUNUCHS AND NON-CASTRATE MALE SUBJECTS. *R. H. Furman, R. P. Howard, M. R. Shetlar and R. Imagawa.* Cardiovascular and Endocrinology and Metabolism Sections, Oklahoma Medical Research Foundation, Dept. of Medicine and Biochemistry, Univ. of Oklahoma School of Medicine, and the Research Laboratory, V. A. Hospital, Oklahoma City, Okla.

Eunuchs manifest less coronary atherosclerosis than non-castrate men. This prompted a study of twenty-four eunuchs and twenty non-castrate

males. The mean age of the eunuchs was thirty-nine, control subjects, forty-one. The data are compared according to three age intervals as well as irrespective of age. Lipoproteins were determined refractometrically.

Castrate men had higher levels of high density (alpha) lipoproteins, higher values for the alpha/beta lipoprotein ratios and lower levels of lower density (beta) lipoproteins than did non-castrate control subjects. Cholesterol levels were significantly higher in the control subjects only in the twenty-one to thirty age group. No differences were noted in phospholipid levels. Urinary 17-ketosteroids were significantly higher in the control subjects. Significantly higher serum glycoprotein levels and glycoprotein/total protein ratios were noted in the castrate subjects.

Androgen loss following castration results in changes in serum lipoproteins resembling those seen in women or following estrogen administration or androgen withdrawal. Castration appears to eliminate the increase in lower density (beta) lipoproteins and the fall in the ratio of high to low density lipoproteins which occurred in the control subjects passing from youth to middle age. The serum lipid pattern distinguishing the eunuch from the non-castrate subject may be importantly related to the eunuch's relative freedom from significant coronary atherosclerosis.

COMPARATIVE ANDROGENICITY OF ORAL ANDROGENS, DETERMINED BY STEROID-INDUCED DECREMENTS IN HIGH DENSITY (ALPHA) LIPOPROTEINS. STUDIES UTILIZING TESTOSTERONE, METHYLTESTOSTERONE, 19-NORTESTOSTERONE, 17-METHYL NORTESTOSTERONE AND 17-ETHYL NORTESTOSTERONE. *R. H. Furman, R. P. Howard, C. W. Smith and L. N. Norcia.* Cardiovascular and Endocrinology and Metabolism Sections, Oklahoma Medical Research Foundation, and the Dept. of Medicine and Biochemistry, Univ. of Oklahoma School of Medicine, Oklahoma City, Okla.

Current interest in 19-nortestosterone and its C-17 derivatives stems from the suggestion that they are anabolic but only weakly androgenic. Review of data obtained during a study of the effects of gonadal steroids on serum lipids permits comparison of the following oral androgens: unmodified testosterone (sublingual), methyl testosterone, 19-nortestosterone, 17-methyl and 17-ethyl nortestosterone.

The concentration of high density alpha lipoproteins ($-S_{1.21}$ 0-12) is regularly reduced by small doses of androgenic steroids. To enhance the sensitivity of this index of androgenicity, only hypogonadal subjects were utilized. Data are taken from sixteen subjects, eight of whom were treated with two or more of these steroids. Review of the data reveals that sublingual testosterone (in doses up to 96 mg./day) produced non-significant decrements in the high density lipoproteins. Methyl testosterone, 17-methyl and 17-ethyl nortestosterone produced prompt and significant reduction in high density lipoprotein concentrations, while 19-nortestosterone was considerably weaker in this regard, but definitely more androgenic than sublingual testosterone. It appears that, by the test of androgenicity employed here, methyl testosterone is the most potent androgen of the group studied, followed closely by 17-methyl and 17-ethyl nortestosterone. Nortestosterone appears to be weakly androgenic, and sublingual testosterone virtually devoid of effect in the doses employed.

EFFECTS OF O_2 BREATHING UPON THE SICKLING PHENOMENON IN VIVO IN SICKLE CELL ANEMIA AND ITS VARIANTS. *E. R. Halden, B. J. Sproule, R. L. Clarke, E. E. Muirhead and W. F. Miller.* Dept. of Medicine, Cardio Pulmonary Laboratory, and Department of Pathology, Univ. of Texas Southwestern Medical School, Dallas, Texas.

Thirteen patients (8 SS, 2 SA, 3 SC) breathed various concentrations of oxygen (9–100%) for thirty to sixty minutes. Arterial and venous blood was obtained for oxygen content, pO_2, pH, percentage sickling (fixation technic) and serum hemoglobin determinations. Blood pO_2 was measured by microbubble equilibration and/or polarography.

With pH usually in physiologic range, per cent sickling was related to change in pO_2. Two groups of curves, suggestively sigmoid in contour, were observed with SA and SC in one group and SS in the other. At high O_2 tensions a few sickle cells remained. The mean arterial pO_2 and saturation in room air were 63 mm. Hg and 89 per cent, respectively. With one exception serum hemoglobin during low O_2 breathing, at the point of maximum sickling, revealed no change from control levels. The serum hemoglobin was not elevated in six patients during crisis. There was no indication of crisis at any O_2 tension.

These results support a relationship between the pO_2 and *in vivo* sickling. *In vivo* sickling alone does not provoke a crisis.

STEROID METABOLISM IN MAN: HYDROCORTISONE OUTPUT OF ADRENAL GLANDS. *James D. Hardy and M. Don Turner, with the technical assistance of Thelma Carter and Virginia Ward.* Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

At laparotomy timed collections of blood flow were taken from the left central adrenal vein (which represents virtually the entire venous drainage of this organ), and free and conjugated hydrocortisone values were compared with those in systemic blood in ten patients. The average measured adrenal vein blood flow was 25 cc./min., the average adrenal venous plasma level of free hydrocortisone 224 gamma per cent, and the average of conjugated hydrocortisone 125 gamma per cent. In systemic blood the average preoperative values for free and conjugated forms were 5.6 and 7.8 gamma per cent; 24.0 and 16.7 during operation; and 9.9 and 25.2 gamma per cent for free and conjugates, respectively, four hours after operation. The relative preponderance of conjugated forms postoperatively perhaps reflected the rapid conjugation of the large amount of free hydrocortisone secreted by the adrenal cortices during operation.

It is estimated on the basis of plasma values that during operation the combined hydrocortisone output of both adrenals was 77 gamma per minute, red cell steroid content not considered. The hydrocortisone output by both adrenals was estimated on the basis of plasma values to be 34 mg. per twenty-four hours. The methods of Nelson and Samuels, and of Bongiovanni were employed.

DEVELOPMENT OF A TECHNIC FOR PHOTOGRAPHIC MEASUREMENT OF BLOOD OXYGEN SATURATION. *J. B. Hickam and R. Frayser.* Dept. of Medicine, Duke Univ. School of Medicine, Durham, N. C.

This communication describes a method for measuring photographically the per cent oxygen saturation of blood in thin-walled vessels which, it is undesirable to traumatize, in particular the vessels of the optic fundus. The method employs the principle that per cent oxygen saturation of blood can be related to the relative intensities of reflected red and infra-red light. Relative light intensities are determined from the densities of the images produced on infra-red sensitive film when pictures are taken of a blood surface. To obtain red and infra-red light densities on a single exposure, a compound filter is used consisting of narrow alternating strips of appropriate Wratten filters. To allow density measurements on structures the size of a retinal vein, considerable enlargement of the original negative is required. To test the principle, photographs were taken of thirty-nine samples of blood from nine normal subjects. The per cent oxygen saturation of these samples, which ranged from 50 to 100, bore a useful linear relationship to the difference between the film densities produced by red and infra-red light. The standard deviation from regression was 4.5 per cent saturation for the original negatives and 6.4 per cent for 8-diameter enlargements. Work is under way to adapt this technic to fundus photography.

HEMORRHAGIC ENCEPHALITIS IN CHICK EMBRYOS INFECTED WITH INFLUENZA VIRUS. *Edward W. Hook and Robert R. Wagner.* Dept. of Medicine, Johns Hopkins Univ. School of Medicine, Baltimore, Md.

Burnet and Fraser described intense cerebral hemorrhages in chick embryos inoculated with a neurotropic strain of influenza virus (NWS). The striking appearance and reproducibility of these lesions afforded an ideal experimental approach to the problems of host susceptibility to virus action. Our studies indicate that the incidence of hemorrhagic encephalitis is profoundly influenced by age of the embryo, route of inoculation, site of viral multiplication, and prior exposure to an interfering virus.

The hemorrhagic effect of NWS virus was greatest in embryos twelve to fourteen days of age; younger and older embryos were comparatively resistant. Intravenous injection of small doses of virus regularly produced infection and hemorrhage of the brain. Virus injected by other routes had limited access to the circulation and was far less pathogenic. Prior allantoic infection with non-neurotropic influenza virus partially counteracted the lethal effect of subsequent intravenous challenge with NWS virus and almost completely prevented the development of cerebral hemorrhages. Allantoic injection of heated virus conferred only partial protection and typhoid vaccine was without effect. Resistance to hemorrhagic encephalitis by concurrent infection at a distant

site appears to be a unique example of the viral interference phenomenon.

ELEVATION GRADIENT OF INTRATHORACIC PRESSURE. *John J. Krueger, John L. Patterson, Jr. and Thomas H. Bain.* Medical College of Virginia, Richmond, Va.

Intrathoracic pressure represents a basic element in the mechanics of breathing. Conventional technic requires the production of a degree of pneumothorax and precludes measurements in multiple areas. In the present studies a localized mobile "pneumothorax" was utilized. A 1.5 cc. thin rubber balloon containing 0.5 cc. air and attached to a 1 mm. ID polyethylene tube was introduced into the intrapleural space through a tightly sealed trocar inserted either at the lung apex or in the third intercostal space and passed down the lateral lung surface to the base. Eleven dogs were suspended in the upright position and pressure continuously recorded during step-wise elevation of the balloon's position.

Despite some individual variation, the mean intrathoracic pressure fell linearly with distance from the lung base. The pressure gradient was 0.21 cm. H_2O/cm. elevation. In two dogs, specific gravity of the lungs in the end tidal position averaged 0.22. Specific gravity of human lungs calculated from standard values for functional residual capacity and total lung weight was 0.21. It is concluded that intrathoracic pressure varies with elevation as would the pressure in a hypothetic fluid of the same specific gravity as the lungs. Intrathoracic pressure in man upright should be 5 cm. H_2O lower at the apex of the lung than at the base. Certain clinical phenomena, such as the greater incidence of bullae at the apexes, are clarified.

PHOSPHATE CLEARANCE IN PARATHYROID DISORDERS. *Laurence H. Kyle, Marcus Schaaf and John J. Canary.* Dept. of Medicine, Georgetown Univ. Medical Center, and District of Columbia General Hospital, Washington, D. C.

Further experience with measurement of tubular reabsorption phosphate (per cent TRP) has substantiated its value in the diagnosis of hyperparathyroidism, but the magnitude of phosphate reabsorption in the normal subject is such that further increase is of little diagnostic significance in parathyroid deficiency. Study was therefore made of the value of measurement of phosphate clearance (Cp) in the diagnosis of parathyroid dysfunction. Phosphate clearance, measured in the fasting state during the forenoon, was 10.8 ± 2.7 ml./min. in the normal subject. Ten patients with hypoparathyroidism had clearance values of 1.7 to 7.3 ml./min.; no significant difference was noted after treatment with vitamin D_2 or AT-10. Similar low Cp was noted in uremia; no rise resulted from parathyroid hormone whereas in hypoparathyroidism Cp rose to normal levels. In six cases of hyperparathyroidism, values ranged from 12.8 to 40.0 ml./min., the single normal value being associated with severe impairment of glomerular filtration. Following removal of a parathyroid tumor per cent TRP rose and the elevated Cp fell rapidly to levels characteristic of hypoparathyroidism. Deprivation of phosphorus, by means of aluminum hydroxide ingestion, in hyperparathyroidism caused rise of per cent TRP and fall of Cp to normal levels.

Measurement of phosphate clearance appears to be of significant diagnostic aid in hypoparathyroidism, and should serve as a valuable screening test for hyperparathyroidism.

FAILURE OF RENAL RESPONSE TO ACETAZOLAMIDE AND TO MERALLURIDE IN A DOG WITH CHRONIC NEPHRITIS. *Thomas H. Maren.* Experimental Therapeutics Section, Research Division, American Cyanamid Company, Stamford, Connecticut.

A case of advanced nephritis in a nine year old female beagle was studied, with particular reference to response to a carbonic anhydrase inhibitor, acetazolamide, and a mercurial diuretic, meralluride. This dog was born and raised in the colony of these laboratories, and its history known. Two years before the present study the dog appeared well and responded normally to acetazolamide. A disease compatible with canine interstitial nephritis appeared spontaneously in the seventh to ninth year of life. Glomerular filtration rate and renal blood flow were 5 to 10 per cent of normal, and blood phosphorus (4 mM./L.) and urea nitrogen (145 mg. per cent) were high. Other chemical findings were not markedly abnormal. Both intravenous acetazolamide (5 mg./kg.) and meralluride (0.08 ml./kg.) failed to produce their typical renal effects. At autopsy, carbonic anhydrase and glutaminase were found in the kidney. Drug failure is provisionally attributed to the low filtration rate of HCO_3^- and Cl^-; it is probable that the (facultative ?) reabsorption

of such small quantities of these ions cannot be influenced by these diuretics.

VALUE OF SPLEEN LOCALIZATION OF CHROMIUM^{51} TAGGED RED CELLS IN SELECTION OF PATIENTS FOR SPLENECTOMY. *Paul R. McCurdy, Charles E. Rath and Benedict J. Duffy, Jr.* Dept. of Medicine, Georgetown Univ., Washington, D. C.

The technic of body surface counting following the injection of Cr^{51} tagged red cells permits localization of the sites of sequestration and destruction of erythrocytes. The cells are tagged with 100 microcuries of Cr^{51}. Following injection of the tagged erythrocytes, the splenic area is monitored until equilibrium is reached according to the technic of Motulsky (modified). Body surface count ratios are determined on subsequent days according to Jandl.

This method has been evaluated in twelve patients with varying degrees of hemolysis. The conditions studied include hereditary spherocytosis, autoimmune hemolytic anemia and abnormal hemoglobin syndromes. In four of the patients splenectomy was performed; three have improved. These patients had maximum spleen/precordium ratios of 1.5 or more and increases in spleen/precordium ratios over the initial readings (sequestration index) of 0.5 or more. The unimproved patient had a maximum spleen/precordium ratio of 0.7 and a sequestration index of 0.25. Improvement following splenectomy coincides with the results predicted. In five of the remaining eight patients the test results did not favor splenectomy. Two of the others are now being prepared for surgery.

It is concluded that the technic of body scanning described may be helpful in selecting patients with hemolytic anemia for splenectomy.

METABOLIC EFFECTS OF ACETIC ACID ANALOGUES OF THYROXIN AND TRIIODOTHYRONINE. *Jean H. McNeil, Samuel B. Barker, Lester L. Hibbett and S. Richardson Hill, Jr.* Dept. of Medicine and Pharmacology, Medical College of Alabama, and Medical Service, V. A. Hospital, Birmingham, Ala.

Reported unique actions of the acetic acid analogues of 3,5,3′ triiodothyronine and thyroxin *in vitro* and in experimental animals have not been corroborated. Previous studies in man have confirmed the thyro-activity of these compounds but have suggested a qualitative difference in their effect on the basal metabolic rate and serum cholesterol level.

The present studies were designed to evaluate further in both experimental animals and in man the metabolic actions of 3,5,3′ triiodothyroacetic acid (Triac) and 3,5,3′,5′ tetraiodothyroacetic acid (Tetrac) and to compare their effects qualitatively and quantitatively with those of thyroxin and 3,5,3′ triiodothyronine (Trit). The studies in experimental animals have demonstrated quantitative but no qualitative differences in the actions of Triac and Tetrac from those of thyroxin or triiodothyronine. No qualitative differences in action have been noted following the oral administration of Triac and Tetrac to myxedematous patients. Decreases in the serum cholesterol level prior to an increase in basal metabolic rate have been noted following the administration of Trit as well as Triac and Tetrac. The relative quantities required for maintaining euthyroidism in these patients are as follows: desiccated thyroid, 90 mg., L-thyroxine, 0.3 mg., Trit, 0.09 mg., Triac, 6.0 mg., and Tetrac, 8.0 mg. As would be anticipated, the serum protein-bound iodine level is disproportionately higher than the metabolic state following the administration of thyroxin, Triac and Tetrac and lower following the administration of Trit.

POTASSIUM CHLORIDE ADDED TO DIETS CONTAINING TOXIC LEVELS OF SODIUM CHLORIDE: HYPERTENSION AND SURVIVAL. *G. R. Meneely, C. O. T. Ball, W. J. Darby, J. Lemley-Stone, R. G. Tucker and J. B. Youmans.* The Radioisotope Service and the Research Laboratory, Thayer V. A. Hospital, and the Dept. of Medicine, Preventive Medicine and Public Health, and Biochemistry, Vanderbilt Univ. School of Medicine, Nashville, Tenn.

In a series of experiments started in 1951 various levels of NaCl added to purified diets fed to 546 young male rats throughout life produced hypertension and decreased survival proportional to the per cent NaCl. Currently, in three levels of added NaCl the K:Na ratio was brought toward 1.0, and a concurrent control group was fed 5.6, 8.4 and 9.8 per cent NaCl without added potassium chloride. There was no difference in the mean maximum systolic blood pressure (measured from the sixth month) in the sixty rats at the 5.6 per cent level. However, at 8.4 per cent NaCl the difference between the rats eating added potassium, 166 mm. Hg, and their controls, 188 mm. Hg, was highly significant (p less than 0.001). In smaller groups

at the 9.8 per cent NaCl level the respective values were 170 mm. Hg and 184 mm. Hg. Significant survival protection was apparent in the 5.6 and 8.4 per cent NaCl diets. Survival of the rats eating 5.6 per cent NaCl fell to 50 per cent in nineteen months, with 2.8 per cent KCl added 85 per cent survived nineteen months, thus exceeding the survival of all rats fed 0.15 to 2.0 per cent NaCl. Half of the rats eating 8.4 per cent NaCl were dead at sixteen months, with the K:Na ratio brought toward 1.0, at twenty-four months.

VALUE OF CERTAIN VENTILATORY FUNCTIONS AS INDEXES OF MECHANICAL PROPERTIES OF PULMONARY APPARATUS. *William F. Miller and Robert L. Johnson, Jr.* Cardiopulmonary Laboratory, Dept. of Internal Medicine, Univ. of Texas Southwestern Medical School, Dallas, Texas.

Previous studies established normal values for the 0.5 and 1.0 second expiratory capacities (TEC) as reliable measures of velocity of air flow. A specific relationship was found between TEC and vital capacity (VC), thus it becomes more useful for purposes of comparison to express TEC as a percentage of VC. This study was undertaken to ascertain the effects of various disturbances of respiratory mechanics on TEC and VC so that the usefulness of these convenient measures might be enhanced.

Dynamic pulmonary compliance and resistance were measured and compared with TEC and VC; in normal subjects and patients with various pulmonary disorders. VC correlates well with dynamic compliance, thus becoming a function not only of musculoelastic properties but also to a lesser extent viscous resistance. TEC is an extremely sensitive and specific index of changes in pulmonary resistance until such time as resistance becomes very high; then VC also diminishes.

Multiple studies were made to demonstrate relationships during the course of treatment. The same correlations were maintained as in individual cases. Thus measurement and interpretation of TEC and VC, in the light of these findings, is a sensitive, reliable and convenient method for evaluating the character of ventilatory disturbances.

CANCELLATION OF ESOPHAGEAL ELECTROCARDIOGRAMS. *Ralph F. Morton, William E. Romans and Daniel A. Brody.* Cardiovascular Laboratory, Dept. of Medicine, Univ. of Tennessee, Memphis, Tenn.

Cancellation of QRS complexes from infra-transitional, transitional or supra-transitional electrocardiographic levels of the esophageal lumen was performed seventy-eight times in twenty-seven subjects. Of the procedures 41.0 per cent resulted in excellent, 28.2 per cent in good and 15.4 per cent in fair cancellations (Schmitt's classification). The corresponding results for twenty-three right arm cancellations were 78.3 per cent, 13.1 per cent and 4.4 per cent, respectively. In decreasing order of excellence the best esophageal cancellations were obtained at the supratransitional, infra-transitional and transitional levels, respectively.

Because of the proximity of the lower esophageal lumen to the heart, esophageal cancellations cannot be explained on the basis of the equivalent cardiac dipole hypothesis. Therefore we developed a new theory of cancellation, based on lead field theory and illustrated by electrocardiographic models, which satisfactorily explains the cancellation phenomenon and resolves the paradoxic implication of the equivalent cardiac dipole concept that proximity leads are not selectively influenced by local action currents. The new theory shows that cancellation occurs largely because (a) the networks employed are relatively insensitive electrocardiographic leads, and (b) there is prior assurance of complete cancellation at any two desired instants of the QRS cycle. Therefore the phenomenon does not critically support the idea of cardiac dipolarity.

PROTECTIVE EFFECT OF HYPOTHERMIA ON TISSUE DAMAGE FOLLOWING RENAL ISCHEMIA FOR PROLONGED PERIODS OF TIME. *John H. Moyer, Charles Heider and Carroll A. Handley.* Baylor Univ. College of Medicine, Houston, Texas.

The employment of hypothermia during surgical procedures has raised the question of a quantitative estimation of the protective effect of hypothermia against tissue damage due to ischemia. Such an estimation is possible in the kidney by measuring glomerular filtration rate and renal blood flow along with water and electrolyte excretion. Observations have been made in which the renal arteries and aorta proximal to the renal arteries were occluded for periods up to three hours. Observations were made on renal function before and five days after occlusion. The procedure was then repeated

during the hypothermic state (80°F.), employing a different group of dogs. Hypothermia has a definite protective effect against tissue damage resulting from ischemia. It approximately doubles the occlusion time tolerated before renal damage occurs and with prolonged periods of ischemia the degree of damage observed is reduced to 50 per cent or less of that observed following a similar period of occlusion with a normal body temperature.

LIFE SPAN OF ERYTHROCYTE FOLLOWING BILATERAL NEPHRECTOMY: EVIDENCE FOR A RAPIDLY ACQUIRED INTRACORPUSCULAR DEFECT. *E. E. Muirhead, F. Jones, M. Groves and B. Brooks.* Dept. of Pathology, Univ. of Texas Southwestern Medical School, Dallas, Texas.

The shortened life-span of canine red blood cells in the incompatible state and following bilateral nephrectomy was similar, as measured simultaneously by the Ashby and Cr^{51} methods (twelve curves). This supports the validity of the Cr^{51} method in abnormal states of the dog.

Four days after nephrectomy red blood cells tagged with Cr^{51} were injected into a normal dog (compatibility by Coombs' test). In thirty experiments, fifteen curves showed disappearance in ten to twenty days and were mainly linear; ten curves showed disappearance in twenty to forty days and five in forty to eighty days. After disappearance of radioactivity autotransfused recipients' red blood cells gave normal disappearance curves (twelve instances; eighty to one hundred twenty days). Similar shortening of Cr^{51} curves in normal dogs was obtained twenty-four hours and three and four days following nephrectomy (four experiments). The Cr^{51} tagged red blood cells from one normal dog were infused into another dog twenty-four hours after nephrectomy and returned to the original normal environment in twenty-four to forty-eight hours. Shortened life-span curves with a sigmoid tendency were observed (four experiments).

Following renal ablation of the dog the erythrocytes appear to be damaged within twenty-four hours or less as indicated by a shortened life-span measured with Cr^{51}.

A STUDY OF THE MECHANISM BY WHICH PRESSURE BREATHING ALTERS URINE FLOW. *H. V. Murdaugh, Jr. and H. O. Sieker.* Dept. of Medicine, Duke Univ. School of Medicine, and V. A. Hospital, Durham, N. C.

This study was made to elucidate the mechanism by which altered distribution of blood volume affects renal function. Thirteen studies have been completed in five normal subjects. Continuous positive or negative pressure breathing was used to decrease or increase intrathoracic blood volume. Urine volume, urine osmolarity, sodium and potassium excretion, and inulin and sodium para-aminohippurate clearance were determined in control and experimental situations. Positive pressure breathing was instituted during water, alcohol and osmotic diuresis.

Positive pressure breathing during water diuresis decreased urine flow from a mean of 14.5 cc./min. to a mean of 6.6 cc./min., and with alcohol diuresis from a mean of 14.5 cc./min. to a mean of 9 cc./min. No response was noted during osmotic diuresis. Negative pressure breathing was associated with a three-fold increase in urine flow. Glomerular filtration rate and effective renal plasma flow were decreased 10 to 20 per cent at the time of maximum alteration in urine flow with both positive and negative pressure breathing. Measurement of solute and water clearance indicated that the oliguria or diuresis observed under the conditions of the experiment was due primarily to impaired or enhanced water clearance.

The evidence suggests that pressure breathing or altered distribution of blood volume, which is believed to be monitored by intrathoracic receptor areas, initiates alterations in urine flow through hormonal mechanisms, primarily an antidiuretic or antidiuretic-like hormone.

USE OF THE SEMI-SITTING POSITION FOR DELIVERY. *Michael Newton.* Dept. of Obstetrics and Gynecology, Univ. of Mississippi School of Medicine, Jackson, Miss.

The lithotomy position is normally used in this country for the conduct of delivery since it is convenient for maintaining asepsis, for administering anesthesia and for performing operative procedures. In this position the force of the mother's voluntary muscles of expulsion and the effect of gravity are less efficiently utilized than in a sitting or squatting position. The majority of primitive peoples deliver their babies in some form of sitting position, and the everyday functions of urination and defecation, in which the same forces are operative, are commonly performed in the sitting position.

Some of these mechanical advantages can be

retained by fitting an adjustable back rest to the conventional delivery table. In this method the patient's hips lie at the edge of the table, her back and neck are flexed and the stirrups are lowered as far as possible. In a preliminary investigation eighty-six patients who delivered in this manner have been studied. The results indicate that the method is entirely compatible with modern obstetrical care, that the efficiency of the expulsive effort is improved, and that the mother is more comfortable and better able to cooperate in the delivery of her baby.

A COMPARISON OF "EXOGENOUS" AND "ENDOGENOUS" PYROGENS. *Robert G. Petersdorf and Ivan L. Bennett, Jr.* Dept. of Medicine, Johns Hopkins School of Medicine, Baltimore, Md.

The intravenous injection of a pyrogenic bacterial endotoxin is followed by the appearance of a fever-producing substance in the serum of rabbits. Differences in the fevers produced by endotoxin and this serum pyrogen suggest that the latter is of endogenous origin, perhaps a product of injured cells. Because rabbit leukocytes are known to contain fever-producing substances it has been postulated that these cells may be the source of endogenous serum pyrogen. In contrast to the heat stability of endotoxins, leukocyte extracts are inactivated at 90°C.

A study of the effects of heating upon the pyrogenic activity of endotoxins, endotoxins mixed with serum (distilled water added to prevent coagulation by heat), "endogenous" serum pyrogen and leukocyte pyrogen was performed in dogs. Intravenous injection of endotoxin in this animal is followed by the appearance of serum pyrogen similar to that in rabbits. Although bacterial endotoxins in water withstood heating at 90°C., several endotoxins in serum, leukocyte pyrogen and endogenous serum pyrogen were inactivated at this temperature. Although these results indicate that serum and leukocyte pyrogens are qualitatively similar, the possibility that "endogenous" pyrogen is exogenous endotoxin modified by contact with serum is not completely excluded.

MECHANICS OF PULMONARY VENTILATION IN THE AGED. *John A. Pierce and Richard V. Ebert.* Dept. of Medicine, Univ. of Arkansas Medical Center, Little Rock, Ark.

Changes in the lung compartments are known to occur with aging but detailed studies of the mechanics of ventilation have not been reported. The purpose of this study was to obtain such information. Consequently, fifteen consecutive patients, sixty-five years of age or older, were studied during hospitalization for prostatic surgery. The following mean values were obtained: Age, 71.9 years. Vital capacity, 3,603 ml. Total lung capacity, 6,646 ml. Ratio of residual volume to total lung capacity, 45.8 per cent. Maximum breathing capacity, 59.2 L./minute. In thirteen subjects, the mean static compliance was 0.364 L./cm. H_2O at the level of pulmonary mid-capacity. The pressure volume curve of the lung was curvilinear throughout. Compliance was 0.480 L./cm. H_2O at .5 L. below mid-capacity and 0.622 L./cm. H_2O at 1 L. below mid-capacity. The mean functional compliance was 0.193 L./cm. H_2O. The mean linear coefficient of resistance was 1.40 and the quadratic coefficient was 1.17.

These data indicate that aging produces a primary change in the elastic properties of the lung which results in a marked alteration of the pressure volume curve and an increase in the residual volume. This change is diffuse and not associated with airway obstruction or pulmonary disability.

COMPARISON OF TWO CORRECTED VECTORCARDIOGRAPHIC LEAD SYSTEMS WITH THE TETRAHEDRON AND CUBE SYSTEMS IN MAN. *Hubert V. Pipberger.* Cardiovascular Research Laboratory, Dept. of Medicine, Georgetown Univ. School of Medicine, Washington, D. C.

Two "corrected" lead systems (SVEC III and Frank) and two conventional systems (Tetrahedron and Cube) were applied consecutively to thirty-five normal subjects and five patients with cardiac disease. SVEC III served as the reference system since in model studies it exhibits the least sensitivity to dipole shifts.

Configuration of vector loops differed considerably. Correlation with SVEC III was best with Frank, then with tetrahedron, and poorest with cube. To evaluate these differences quantitatively the positive and negative components of x, y and z axes in each of the three latter systems were compared with SVEC III.

The Frank system exhibited reduced magnitude of the z axis and increase of the y axis but with comparable percentage deviations in positive and negative directions. For tetrahedron, positive x, y and z deflections were decreased, negative x, y and z values increased. For cube, positive x and negative z deflections were in-

creased and positive z values were extremely low.

The Frank system could be improved by changing amplification factors since in many instances it would then approach SVEC III results. In the tetrahedron and cube systems amplification changes would not improve results since correction of lead axis in one direction would produce further distortion in the opposite direction. Further, the range of variations was extremely large.

CHANGES IN ENZYME ACTIVITY (GLUTAMIC-OXALACETIC TRANSAMINASE, LACTIC DEHYDROGENASE, CYTOCHROME *c* AND CYTOCHROME OXIDASE) IN SERUM AND HEART MUSCLE AFTER EXPERIMENTAL MYOCARDIAL INFARCTION. *Helmut Redetzki, Arthur Ruskin, Wiktor Nowinski, John Sinclair, Paul Rosenthal and Belle Ruskin.* Dept. of Internal Medicine, the Tissue Metabolism Research Laboratory, and the Dept. of Anatomy, Univ. of Texas, Medical Branch, Galveston, Texas.

Elevations of serum transaminase and lactic dehydrogenase activity have been found to occur after experimental and clinical myocardial infarction. There is also evidence of loss of enzyme activity in infarcted myocardium. We carried out studies of cytochrome *c*, cytochrome oxidase, together with the other enzymes mentioned, following experimental myocardial infarction in dogs.

Satisfactory ligations of the anterior descending branch of the left coronary artery were performed under nembutal anesthesia in fourteen dogs with an average weight of 10 kg. Two dogs died during the operation and two died postoperatively of ventricular fibrillation.

The results showed a marked increase (27–16×) of activities in the serum in the following order: transaminase (average, 663 units), lactic dehydrogenase (average, 4,690 units), and cytochrome *c* (average, 0.45 mg. per cent) with the maximum generally at eight hours and lasting for about forty-eight hours to several days. Secondary rises, apparently not related to the infarct, occurred in some instances in lactic dehydrogenase and cytochrome *c* only. Cytochrome oxidase activity was never demonstrated in the serums, perhaps because of insolubility due to strong binding to the mitochondria. All four enzymes showed a similar decrease in activity (35 to 47 per cent) within the infarcted muscle, in contrast to control samples of the left and right ventricles. For the controls two dogs had sham operations, including thoracotomy and pericardiotomy with the placing of an untied ligature around the descending branch of the left coronary artery. The resulting slight injuries of skeletal and cardiac muscles produced only slight rises (2–5×) in serum enzyme activities.

The release of the various cell proteins and degradation products in myocardial necrosis must be correlated with other biochemical alterations, such as in electrophoretic patterns, sedimentation rate, serum fibrinogen, etc.

OBSERVATIONS OF CARDIOVASCULAR FUNCTION IN HYPOTHERMIC ANESTHETIZED MAN. *John C. Rose, Lawrence S. Lilienfield, Thomas F. McDermott, Frank A. Porfido and Robert T. Kelley.* Depts. of Medicine and Anesthesiology, Georgetown Univ. Medical Center, Washington, D. C.

Hypothermia is employed in patients as an adjunct to general anesthesia, yet few measurements have been made of its physiologic effects in the operating room. Ten patients without cardiovascular disease, undergoing surgery for malignancy, were surface-cooled to 30.5–32.5°C. (rectal). After induction of anesthesia, *before cooling*, tagged albumin indicator-dilution curves were obtained from the femoral artery following antecubital vein injection. Direct intra-arterial pressure pulses were traced. Measurements were repeated *after cooling*, before operation. Cooling period (average two hours) was free of drugs and fluids; no shivering was noted.

The heart rate fell in seven cases (mean 31 per cent), increased in none. Cardiac output fell significantly in five cases (mean 36 per cent) and actually increased in two (29, 23 per cent). Tracings showed prolongation of systole from 32 to 39 per cent of the cycle. The mean arterial pressure rose significantly in seven cases (mean 35 per cent), fell in only three. Total peripheral resistance and cardiac work increased in over half of the cases. The mean circulation time was prolonged in seven cases. Hemoconcentration was observed, as in animal experiments.

The observed variable human vasomotor and cardiac responses to cold are in contrast to the uniform results of laboratory animal studies. The uncontrolled nature of the operating room setting and potential hazards of this procedure are emphasized.

CHANGES IN OLFACTORY ACUITY IN HYPOGONADAL SUBJECTS ACCOMPANYING ANDROGEN AND ESTROGEN ADMINISTRATION. *Robert A. Schneider, J. Paul*

Costiloe, R. Palmer Howard and Stewart Wolf. Oklahoma Medical Research Foundation and the Depts. of Medicine and of Psychiatry and Neurology, Univ. of Oklahoma School of Medicine, Oklahoma City, Okla.

Prior studies demonstrated greater olfactory acuity in women than in men and decreased acuity during menstruation. Olfactory acuity was measured (air-conditioned walk-in type olfactorium) in (1) young oophorectomized and (2) postmenopausal women during intermittent administration of androgens and estrogens. Urinary gonadotropins, 17-ketosteroid excretion and nitrogen balance studies were obtained. Observations were made of color, secretions and swelling of the nasal membranes.

Without treatment olfactory acuity was less in these women than in fifteen young healthy women ($P < .01$). Estrogen administration in two subjects was accompanied by an increase in olfactory acuity compared to control values ($P < .01$). One subject receiving androgen showed decreased acuity ($P < .02$). 17-ketosteroid excretion values compared to acuity values showed high positive correlation in one subject receiving androgen ($P < .01$) and modest correlation in one receiving estrogen ($P < .08$). During androgen administration increased nitrogen retention accompanied decreased olfactory acuity ($P < .01$). During estrogen administration elevated gonadotropin excretion accompanied decreased olfactory acuity ($P < .01$) in one subject. Nasal mucous membranes during control periods were redder ($P < .02$) than in the young healthy women and there was a trend toward shrinkage and dryness. No significant changes accompanied hormonal administration.

Olfactory acuity correlates with gonadal steroid levels. This might explain the sex differences in olfactory acuity.

ROLE OF GLYCOLYSIS IN CHOLESTEROL SYNTHESIS. *Marvin D. Siperstein.* Dept. of Internal Medicine, Univ. of Texas Southwestern Medical School, Dallas, Texas.

Although the factors which control cholesterol metabolism are obscure, it is known that glycolysis definitely influences concomitant cholesterol synthesis. The present study was designed to determine, by using cell-free homogenates of normal rat liver, how the two glycolytic pathways, that is, the Embden-Meyerhof (EM) pathway and the hexosemonophosphate (HMP) shunt, influence cholesterol synthesis and the cofactors which mediate this effect.

Stimulation of glycolysis via the HMP shunt alone accelerated cholesterol synthesis approximately tenfold, whereas stimulation via the EM pathway alone inhibited cholesterol synthesis by rat liver. Cholesterol synthesis during simultaneous stimulation of EM and HMP glycolysis was relatively inhibited as compared with that during HMP shunt stimulation alone. Reduced coenzyme II (triphosphopyridine nucleotide) appears to be the cofactor responsible for the marked enhancement of cholesterol synthesis by HMP glycolysis.

It is concluded that cholesterol synthesis is regulated, in part at least, by the relative amounts of glucose which traverse each of the two glycolytic pathways, that which goes through the HMP shunt stimulating cholesterol synthesis, that which is oxidized via EM glycolysis inhibiting cholesterol synthesis.

DIRECT COOMBS' TEST AND THE RETICULOCYTE. *Donald A. Sutherland, Anna M. Eisentraut and Mary Sue McCall.* Radioisotope Units of the V. A. Hospital and St. Paul's Hospital; Dept. of Medicine, Univ. of Texas Southwestern Medical School, Dallas, Tex.

Reticulocytes can be graded according to the degree of immaturity into types I, II, III, IV. The type of reticulocytes vary according to the degree of nucleoprotein that stains with the brilliant cresyl blue stain. Type I and type II reticulocytes have been tested with anti-globulin (Coombs') serum and have been found to be coated with globulin. Type I and type II reticulocytes are produced usually by brisk hemorrhage with a prompt reticulocytosis. A positive reaction to the Coombs' test may occur in whole blood which is due to these reticulocytes. Splenectomy may cause an elevation in the reticulocyte count and in animals will produce a positive reaction to the Coombs' test due to a high proportion of reticulocytes in the peripheral blood. Studies in man, the rabbit, and in dogs show that reticulocytosis induced by hemorrhage; or in humans following liver therapy for pernicious anemia; or iron therapy for blood loss anemia, is associated with a positive reaction to the direct Coombs' test. The phenomenon of positivity of the blood is only apparent when the reticulocyte fraction exceeds 10 per cent and then the positive reaction to the Coombs' test

is limited to the fraction of blood that has the highest concentration of reticulocytes.

INTRAHEPATIC PORTAL OBSTRUCTION IN WILSON'S DISEASE AS DEMONSTRATED BY HEPATIC VENOUS CATHETERIZATION AND SPLENOPORTAL VENOGRAPHY. *W. Jape Taylor, F. C. Jackson and Wallace N. Jensen.* Depts. of Medicine and Surgery, Univ. of Pittsburgh Medical School, and V. A. Hospital, Pittsburgh, Pa.

Moderate to marked splenomegaly in four patients with hepatolenticular degeneration (Wilson's disease) prompted investigation of the portal circulation in these patients. Hepatic venous catheterization, with blood flow and wedged venous pressure measurements, was performed in all four patients and percutaneous splenic pulp pressures with portal venograms were obtained in three.

In three patients with primarily neurologic manifestations, the wedged hepatic venous pressure was normal (mean 8.0 mm. Hg) whereas in two of these three patients the splenic pulp pressures were elevated (mean 24.5 mm. Hg). The hepatic blood flow and bromsulphalein clearance were normal in these patients. In a fourth patient with long-standing, advanced liver disease the splenic pulp pressure and wedged hepatic venous pressure were elevated to the same degree. The hepatic blood flow and bromsulphalein clearance were low. The three patients who had portal venograms demonstrated patent, abnormally tortuous and dilated portal veins with collateral venous channels.

A normal wedged hepatic venous pressure in the presence of an elevated splenic pulp pressure and a patent portal vein suggests that an intrahepatic presinusoidal block exists early in the course of Wilson's disease. Comparable data are not available in mild Laennec's cirrhosis, but in the more advanced stages of this disease, the splenic pulp pressure and wedged hepatic venous pressure are both elevated; indicating sinusoidal or postsinusoidal obstruction. With progression of the hepatic disorder in hepatolenticular degeneration, obstruction to intrahepatic circulation becomes more widespread, and presumably involves the sinusoidal or postsinusoidal bed, with resultant circulatory dynamics which resemble those of advanced Laennec's cirrhosis.

IN VITRO IRON UTILIZATION BY HUMAN BONE MARROW. *Oscar A. Thorup, Jr., William Earl Strole, Jr. and Byrd S. Leavell.* Dept. of Internal Medicine, School of Medicine, Univ. of Virginia, Charlottesville, Va.

A roller tube tissue culture technic has been applied to study certain aspects of iron utilization by human bone marrow. Using tracer amounts of Fe^{59} the average amount of iron utilized by the erythrocyte precursor in the bone marrow culture was determined (69×10^{-9} gamma) and found to be of the same order of magnitude as the quantity of iron in the mature red blood cell (91 to 108×10^{-9} gamma).

Progressive reduction of iron available in the culture uncovers increasing percentage utilization of iron (10 per cent to 90 per cent) by the erythrocyte precursor while absolute utilization decreases. This inverse relationship suggests that the iron present in serum is readily available to maturing erythrocytes and that the needs of the cell are not compromised by the binding of serum globulin. Above a certain point increase of available iron does not result in increased utilization. The most efficient level of iron utilization in the culture is of the order of 150×10^{-9} gamma Fe per cell.

Application of this method to study of the marrow of patients with uremia has revealed a lower average cellular uptake of iron than normal. This suggests that a defect in hemoglobin synthesis may play a part in the anemia of these patients.

CHOLESTEROL STUDIES IN PATIENTS WITH MYOCARDIAL INFARCTION. *William T. Tucker, John C. Forbes and Paul D. Camp.* Depts. of Medicine and Biochemistry, Medical College of Virginia, Richmond, Va.

Only a small percentage of the total cholesterol is removed when the lyophilized serum of young male subjects is extracted with cold chloroform for a three-hour period. The concentration of this fraction and the total cholesterol were determined in 303 male and 235 female patients without demonstrable heart disease and 214 patients with myocardial infarction. Of fifty-one men with myocardial infarction, aged fifty or less, 71 per cent exhibited elevated three-hour extraction values as compared to 25 per cent of 191 control subjects. Of ninety-five men with myocardial infarction over fifty years of age, only 53 per cent had elevated three-hour extraction values. Of 22 women with myocardial infarction over fifty years of age, 81 per cent showed elevated three-

hour values compared to 36 per cent of ninety-eight control subjects. Total cholesterol was above 300 mg. per cent in 95 per cent of women over fifty years of age with myocardial infarction, as compared to 40 per cent in female control subjects. Sixty-three per cent of male patients under 51 years of age with myocardial infarction had total cholesterol values greater than 300 mg. per cent, compared to only 23 per cent of 191 male control subjects.

Total cholesterol and three-hour extraction fraction measured during the acute stages following myocardial infarction were often low while subsequent determinations showed elevated values. The results emphasize the apparent relationship between cholesterol metabolism and myocardial infarction.

FACTORS CONTROLLING CARDIAC OUTPUT: THE EFFECT OF POSTURE AND ATROPINE. *J. V. Warren, A. M. Weissler and J. J. Leonard.* Dept. of Medicine, Duke Univ. School of Medicine, and V. A. Hospital, Durham, N. C.

It has long been recognized that when the patient is in the passive erect posture the cardiac output is lower than when the patient is in a recumbent position. In an effort to determine whether or not this represents lessened demands on the heart or inability to respond, studies on the effect of alterations in heart rate induced by atropine were undertaken. Three groups of normal male volunteers were studied. In group I cardiac output (dye technic) was determined before and two minutes after 2.0 to 2.8 mg. atropine sulphate was administered intravenously with the subject in a recumbent position. In group II similar studies were carried out with the subject in a 60 degree head-up tilt position. In group III the effect of atropine on induced vasodepressor syncope was observed.

In group I marked increases in cardiac output (74 per cent above control average of 3.0 L. cardiac index) were observed, predominantly the result of increased heart rate. Despite even greater increases in rate, subjects in group II were found to have only slight increases in minute output (12 per cent above control). In syncopal subjects no significant effect on output was observed. These observations are consistent with the thesis that availability of blood is a limiting factor in cardiac output response and, in particular, may explain the reduced output found with subjects in the passive erect posture.

ALIMENTARY LIPEMIA AND CORONARY ARTERY DISEASE IN TWO RACIAL GROUPS. *A. M. Weissler and O. W. Shapiro.* Dept. of Medicine, Duke Univ. School of Medicine, and V. A. Hospital, Durham, N. C.

In an effort to detect and study susceptibility to coronary artery disease, a test of alimentary lipemia has been utilized. This test is based on reported alterations in lipemic response in patients with coronary atherosclerosis. Because of the recognized difference in incidence of this disease in white and Negro races, groups of fourteen patients of each race were studied. They came from a hospital population in which the racial difference in incidence of coronary artery disease was 2.2 white to 1 Negro. The subjects were fasting young male patients without cardiovascular or gastrointestinal disease. The groups were of similar average age and body surface area. Alimentary lipemia was assayed by following the plasma turbidity (Beckman DU spectrophometer at 650 mμ) over a six-hour period following the test meal of 100 cc. of 10 per cent cream per square meter.

The mean fasting and hourly turbidities as well as planimetrically integrated areas under the turbidity curves were compared. No significant differences in the turbidity curves in the white and Negro groups were observed, the two behaving statistically in this respect as if selected from the same population. Individual variation from the normal distribution was likewise not different in the two groups.

CARDIOVASCULAR EFFECTS OF PROVOCATIVE TEST DRUGS USED IN THE DIAGNOSIS OF PHEOCHROMOCYTOMA GIVEN DURING INFUSIONS OF EPINEPHRINE AND NOR-EPINEPHRINE. *Joseph A. Wilber and Albert A. Brust.* Dept. of Internal Medicine, Emory Univ. School of Medicine, and Grady Memorial Hospital, Atlanta, Ga.

Since provocative test drugs are widely employed in suspected pheochromocytoma, this study was designed to clarify the actions of these agents in the presence of known amounts of circulating catecholamines. In twenty-one fasting normotensive subjects, auscultatory blood pressures and pulse responses to histamine base (0.025 mg. intravenously), mecholyl (10 mg. subcutaneously), tetraethylammonium chloride (TEAC 400 mg. intravenously) and atropine sulfate (1.2 mg. intravenously) were recorded during control periods, during constant infusion

of L-epinephrine (0.085 μg./kg./min.) and of L-nor-epinephrine (0.085 μg./kg./min.).

Both TEAC and atropine markedly potentiated the pressor response to nor-epinephrine (TEAC, +33/20 mm. Hg; atropine, +45/35 mm. Hg) but did not potentiate epinephrine. Mecholyl and histamine were consistently depressor during epinephrine and nor-epinephrine infusions.

In twelve subjects, cardiac outputs were measured before and after potentiation of nor-epinephrine by TEAC or atropine. In all cases in which blood pressure was potentiated, the cardiac output increased significantly (atropine, 2.4 L./min.; TEAC, 1.38 L./min.). Peripheral resistance was unchanged or decreased.

The results suggest: (1) In pheochromocytoma a positive provocative test with TEAC represents a potentiation phenomenon specific for circulating nor-epinephrine. (2) Atropine, like TEAC, potentiates nor-epinephrine and should be evaluated as a screening agent for pheochromocytoma. (3) Pressor potentiation of nor-epinephrine by TEAC or atropine is probably due to blockade of carotid sinus and aortic arch reflexes controlling cardiac rate and not to changes in peripheral resistance.

RESPIRATORY ALKALOSIS AS A RESULT OF ADMINISTRATION OF 2,4-DINITROPHENOL. *T. F. Williams, R. W. Winters, J. R. Clapp and L. G. Welt.* Dept. of Medicine, Univ. of North Carolina School of Medicine, Chapel Hill, N. C.

2, 4-dinitrophenol (DNP) is known to produce an increase in metabolic rate and a concomitant increase in pulmonary ventilation. This hyperventilation has been assumed to arise from chemical stimuli secondary to the accelerated metabolic rate. Data which raise questions about this assumption have been collected in the course of studies of the effect of DNP on renal tubular reabsorption of water. Dogs were given DNP, 5–10 mg./kg. intravenously. Marked hyperventilation began immediately and continued several hours. Arterial blood, sampled before and 5 to 140 minutes after injection of DNP, showed a rise in pH and fall in pCO_2 (calculated from pH and CO_2 content, corrected to 38°C.) in every instance, before any significant change in body temperature. Mean maximal changes in four unanesthetized dogs, expressed as before/after DNP, were pH 7.385/7.490, pCO_2 37.3/29.0 mm. Hg. Three animals under pentobarbital anesthesia showed changes of similar magnitude.

DNP thus induces such marked hyperventilation that respiratory alkalosis results. It is suggested that this degree of hyperventilation cannot be simply secondary to increased production of CO_2 but probably also reflects a direct effect of DNP upon the respiratory center or its peripheral afferent connections.

PHYSIOLOGIC OBSERVATIONS EMPLOYING BUBBLE-TYPE PUMP OXYGENATOR. *William T. Williams.* Dept. of Surgery and the Surgical Research Laboratory, Univ. of Mississippi Medical Center, Jackson, Miss.

This communication deals with various physiologic observations made during the use of a bubble-type pump oxygenator during complete by-pass of the heart and lungs in thirty dogs. The pump oxygenator employed is, with a few minor modifications, similar to that developed by DeWall in Minneapolis.

The following observations will be presented and briefly discussed: (1) pH—a constant decrease in plasma pH but lack of correlation with the amount of pump blood flow. (2) Platelets—a constant decrease and again lack of correlation with blood flow. (3) Arterial and venous oxygen and carbon dioxide saturations determined "pre-run," "mid-run" and "post-run" employing various oxygen and blood flow rates. (4) Sodium—an unexplained frequent but variable decrease. (5) Potassium—an almost constant increase.

EXPERIMENTAL CORONARY ARTERY OCCLUSION: VENTRICULAR FIBRILLATION AND SURVIVAL AS AFFECTED BY SELECTED DRUGS AND IONIC ALTERATIONS. *William T. Williams, Albert L. Meena and James D. Hardy.* Dept. of Surgery, Univ. of Mississippi Medical Center, Jackson, Miss.

This report concerns myocardial ischemia in forty-three dogs, and the influence of drugs and inorganic ions on fibrillation and survival rates. Ischemia was accomplished by placing a loose ligature beneath the anterior descending branch of the left coronary artery and occlusion of the artery by tightening the ligature one to several days subsequently. Values for plasma pH, CO_2, potassium, sodium, chloride and calcium were secured as controls and following infusion of the ions and drugs employed. Electrocardiograms were obtained pre- and postocclusion.

The animals were divided into the following

groups: (1) control group, and ten animals with occlusion on the first postoperative day; (2) control group, and three animals with occlusion twenty days postoperatively. The following groups each contained five animals in which occlusion occurred one day postoperatively: (1) acidosis (hydrochloric acid); (2) alkalosis (sodium bicarbonate); (3) hyperkalemia; (4) hyperpotassemia; (5) excess sodium chloride; and (6) procaine

The results concerning ventricular fibrillation and survival are as follows. In the control group with occlusion on the first postoperative day the mortality rate was 80 per cent with three of ten animals experiencing ventricular fibrillation. There was no fatality or electrocardiographic change in two dogs with occlusion twenty plus days postoperatively. Acidosis: 80 per cent mortality, 40 per cent ventricular fibrillation; alkalosis: 80 per cent mortality, 60 per cent fibrillation; hyperpotassemia: 60 per cent mortality, 60 per cent fibrillation; hypercalemia: 80 per cent mortality, 60 per cent fibrillation; excess sodium chloride: 100 per cent mortality, 80 per cent fibrillation; procaine: 100 per cent mortality, 100 per cent fibrillation.

A surprising decrease in serum sodium and potassium was noted after intravenous administration of calcium chloride and these findings, along with an analysis of the pH, CO_2, chloride and calcium values and interpretations of the electrocardiograms, will be presented.

OBSERVATIONS ON THE PLASMA CARBON DIOXIDE TENSION DURING RECOVERY FROM DIABETIC AND DIARRHEAL ACIDOSIS. *Robert W. Winters, John A. Lowder and Nelson K. Ordway*. Depts. of Pediatrics and Medicine, Univ. of North Carolina School of Medicine, Chapel Hill, N. C., and Dept. of Medicine, Univ. of Alabama, School of Medicine, Birmingham, Ala.

Serial observations of whole blood pH, plasma total CO_2 content and calculated plasma carbon dioxide tension (pCO_2) have been made in ten children and one adult recovering from diabetic acidosis and in twenty-nine infants and children recovering from diarrheal acidosis. The data show that recovery of most of the patients in both groups (nine of the diabetic subjects and twenty-three of the patients with diarrhea) includes a phase in which the blood has become either normal or alkaline while the pCO_2 is still depressed. These observations demonstrate sustained hyperventilation on the part of such patients in spite of the absence of recognized chemical stimuli producing augmented ventilation.

The finding of this pattern of recovery in these two types of metabolic acidosis, as well as observations of a similar type by others in patients with uremic acidosis and ammonium chloride acidosis, suggests that delayed recovery of normal pCO_2 may be common to all types of metabolic acidosis. It is suggested that an increased sensitivity of the respiratory center to the stimuli of pCO_2 and/or hydrogen ion may account for these findings.

RELATIONSHIP BETWEEN BLOOD PCO_2 AND THE CARDIAC TOXICITY OF POTASSIUM. *Daniel T. Young, Edwin W. Monroe and Ernest Craige*. Dept. of Medicine, Univ. of North Carolina School of Medicine, Chapel Hill, N. C.

Dog heart-lung preparations were used to study the effect of alterations of blood pCO_2 on the cardiac toxicity of potassium. In seven preparations with serum potassium elevated by infusion (average 8.3 mEq./L.) electrocardiographic abnormalities appeared following a drop in pCO_2 from 120 mm. Hg to 30 mm. Hg. In five of these the electrocardiographic abnormalities were reversed by raising pCO_2, and the cycle was repeated. Serum potassium was constant. Five preparations subjected to identical changes in pCO_2 but with normal potassium showed no important electrocardiographic abnormalities. Serum calcium and protein remained constant in all experiments.

Elevation in pCO_2 from normal to about 120 mm. Hg produced both cardiac dilatation and rapid drop in cardiac output. Partial recovery ensued in approximately fifteen minutes if acidosis persisted, but immediate recovery followed return of pCO_2 to normal. In dogs with elevated potassium this improvement lasted only until electrocardiographic deterioration began. In dogs with normal potassium, improvement persisted.

Conclusions: In this preparation, high pCO_2 ameliorates the cardiac toxicity of potassium. High pCO_2 quickly decreases the force of ventricular contraction, an abnormality partially compensated at high pCO_2 and reversed by return to normal pCO_2. Changes in potassium and pCO_2 may cause certain post-hypercapneic arrhythmias. Additional factors probably operate in intact animals.

HEPATITIS DUE TO THE PSITTACOSIS VIRUS OCCURRING DURING AN EPIDEMIC AMONG TURKEY

HANDLERS. *E. M. Yow, Jane Preston and R. D. Leachman.* Dept. of Medicine, Baylor Univ. College of Medicine, the Medical Service of the Jefferson Davis Hospital and the Ben Taub Research Laboratory, Houston, Tex.

An outbreak of psittacosis occurred among the employees of two poultry produce houses, resulting in twenty-four cases and one death. The source of infection in this epidemic was traced to one flock of turkeys which was dressed and cleaned by both companies. Turkeys have become increasingly important in the transmission of psittacosis to humans in this area. The attack rate was highest among those employees who handled the live birds. In two of the most severely ill patients jaundice and oliguria developed in addition to a pneumonitis. One of these two patients recovered, the other died. Postmortem examination revealed extensive interstitial pneumonia with thick, gelatinous material obstructing many of the smaller bronchioles; the liver showed focal necrosis and the kidneys showed degeneration of the proximal tubules and plugging of the tubules with bile and leucine crystals. Liver function studies in these two patients were indicative of hepatocellular disease. Review of the literature has failed to disclose previous reports of jaundice and oliguria in psittacosis.

Case Reports

An Unusual Case of Acute Porphyria with Volvulus and Gangrene of the Cecum*

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ABDOMINAL pain and bowel distention are well known features of intermittent acute porphyria. Bowel obstruction has often been simulated, obstipation is often severe and the x-ray film of the abdomen may reveal surprising degrees of bowel distention especially of the colon beneath the left leaf of the diaphragm [*1,2*]. These points have often been emphasized and it has generally been assumed that if the diagnosis of porphyria is confirmed by the history and adequate examination of the urine, conservative management is in order. The purpose of the present report is to point out that, on occasion, mechanical disturbances secondary to porphyria may result in severe acute changes in the bowel urgently requiring surgical treatment to prevent a fatal outcome.

CASE REPORT

S. F. (U. H. No. 868284), a forty-seven year old farm housewife, was admitted on March 15, 1954, with the present complaint of vomiting, weakness and abdominal pain for ten days.†

The patient began to vomit, without known cause, on March 5, 1954. The next day her three and one-half year old son was ill with a laryngeal obstruction and she stayed up all night to care for him. On March 7 the boy was taken to the local hospital and a tracheotomy was performed. The patient did not feel well but did not vomit again until March 8. She had had a dull, rather generalized abdominal pain since the outset, more marked in the suprapubic area. Because of continued vomiting, pain and "grogginess" she was admitted to the local hospital on March 9 under the care of Dr. Leon E. Steiner of Albert Lea, Minnesota. Dr. Steiner called one of us (C. J. W.) on March 12 to request transfer of the patient to the University Hospital. Dr. Steiner had established the diagnosis of porphyria by noting that the patient's urine was red and that it exhibited intense red fluorescence under ultraviolet light. On March 12 the patient's condition was believed to be relatively good but on March 15 her pain was much more severe and, as will be noted in the following, her condition had become very poor at the time of admission to University Hospital. She had had but one bowel movement in ten days; this was on March 12 following an enema.

The past history revealed that the patient had had two episodes of vomiting, both in relation to pregnancy, the first for two weeks early in the first pregnancy. She ascribed this episode to fumes from new paint in her house. During her fourth pregnancy she had nausea and some vomiting for about four months, mainly induced, she stated, by the smell of food. There had been six pregnancies and six living children, all well (v. seq.). As a child the patient had mumps, measles and chicken pox, and pleurisy in her teens. She denied other illnesses. The menarche was at the age of twelve, the periods were always regular and normal at a twenty-eight to thirty-day interval, of four days' duration with very little dysmenorrhea. The last period began about March 10, 1954, during the week prior to admission to our service.

The family history was essentially unrevealing. The patient had had eleven siblings. One brother died at the age of thirty-nine following an operation for a "twisting of the bowels." He had had an undiagnosed abdominal pain for one month, after which operation was said to have revealed the condition just mentioned. He was apparently improving after the operation but died suddenly due to a "blood clot." Five other siblings had died of various unrelated causes.

The patient had never observed any weakness or pain in the extremities. In recent months there had been a mild increase in nocturia and difficulty in

† We are indebted to Dr. Leon Steiner of Albert Lea, Minnesota for referring this patient to the University Hospital, and his cooperation in providing valued information.

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starting the flow of urine, with moderate urgency but no dysuria, increased frequency or polyuria.

The patient had not observed any undue sensitivity of the skin to light. There was no history of blisters, urticaria or rashes on sun exposure, or of the appearance of blisters following trauma or heat.

On admission on March 15, 1954, at 3:00 P.M., the patient was acutely ill, with marked abdominal distress and considerable distention. The pulse was weak, 130, with regular rhythm. The oral temperature was 98.6°F. The blood pressure was 80 (palpation only). Except for the general appearance and circulatory findings only the abdomen was abnormal. It was moderately distended, tense, tympanitic, intermittently rigid, diffusely tender but without definite rebound tenderness. There were no abnormal neurologic findings. A urine sample obtained shortly after admission revealed a strongly positive porphobilinogen reaction. (See Table 1 for porphobilinogen and porphyrin data.) Some peculiar features of the porphobilinogen in this case will be described later. The urine was normal in all ordinary respects.

The initial leukocyte count was 8,200 per cu. mm. with 70 per cent neutrophils, 24 per cent lymphocytes, 6 per cent monocytes. The hemoglobin was 16.3 gm./100 cc. The serum sodium was 134 mEq./L., potassium 4.4 mEq./L.

A flat film of the abdomen revealed "a distended viscus in the left upper quadrant of the abdomen, most likely representing a greatly distended cecum." The possibility of volvulus of the cecum was suggested.

The patient was given saline solution and glucose intravenously and inlying nasal gastric suction was started. Levophed® was given and the blood pressure rose to a normal range, fluctuating in the next few hours between 100–160/80–120. The patient appeared to improve temporarily but between 12 and 2 A.M. her temperature rose rather abruptly to 105°F., the abdominal distention increased, the pulse rate increased and the blood pressure was 90–100 systolic. The leukocyte count at 3 A.M. was 8,600 per cu. mm. Another flat film of the abdomen showed increased distention of the involved loop. It now measured 19 cm. at its widest diameter, from mid-abdomen to splenic flexure. (Fig. 1.) No gas could be seen in the rectum. The blood urea nitrogen was 53 mg./100 cc.; CO_2 19 mEq./L., chlorides 102 mEq./L., sodium 143 mEq./L. Shortly before 6 A.M. the patient became much worse, was obviously in shock, with blood pressure unobtainable. She was given one unit of blood, 20 mg. of vasoxyl® and another ampule of levophed, and after forty-five to sixty minutes her blood pressure was recorded between 90–100. She was at once taken to the operating room and laparotomy by one of us (R. L. V.) was carried out under local anaesthesia. The operative report follows:

"On opening the peritoneal cavity it was evident that there was a large segment of gangrenous bowel and that this involved the cecum, ascending colon and

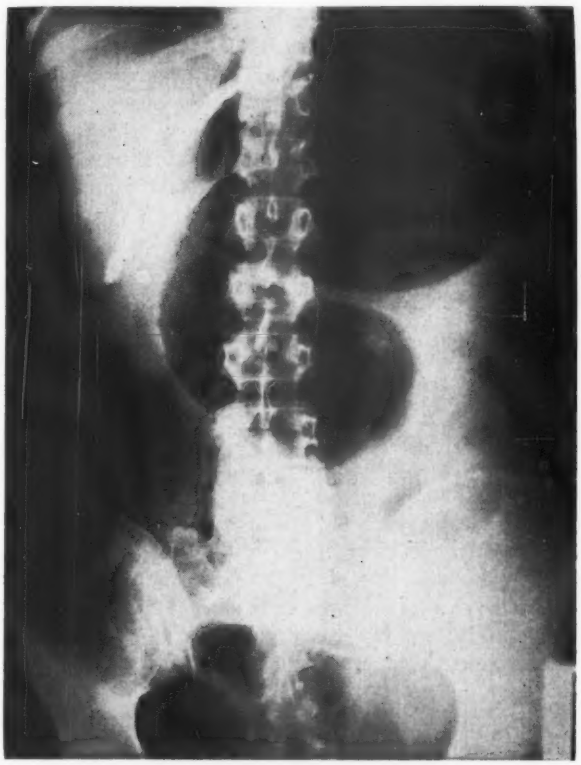

FIG. 1. Preoperative flat film of abdomen to show extreme distention of colon. At operation this was revealed as the volvulus of the cecum.

a portion of the terminal ileum. It had turned on itself towards the left upper quadrant and then was rotated through approximately 360° being torsed and strangulated with the bowel gangrenous throughout this entire area. After identifying the pedicle of this area of volvulus and strangulation and compressing the pedicle with my hand, the bowel was then delivered and no venous blood allowed to return from the strangulated bowel as it was delivered from its position in the left upper quadrant. Clamps were then placed directly across the terminal ileum, the blood supply to the terminal ileum, the blood supply to the right colon and the ascending colon and this segment of gangrenous bowel cut off between clamps, following which the blood vessels to this area were identified and stick-tied. The ileum and colon were then resected to the area where there was a good blood supply. With a rubber shod clamp in place to hold the intestinal contents from the terminal ileum, a single row anastomosis was made using 4-0 silk. The mesentery to the terminal ileum, was then approximated to the colon in the region of the hepatic flexure. The width of the anastomosis, in excess of 5 cm., was made using oblique placement of the clamps on both the colon and the small bowel. Having completed this anastomosis, making sure that there was a patulous lumen, the peritoneal cavity was aspirated of all clots and residual free

fluid. There had been a considerable amount, with a strong odor suggestive of necrotic bowel, found at the time the abdomen was opened. After having cleaned out the peritoneal cavity thoroughly the wound was washed with two liters of cool 5 per cent glucose in distilled water. This was all aspirated carefully then with the suction-tip and neomycin in the amount of 1 gm. in solution deposited throughout the peritoneal cavity particularly in the region of the left upper quadrant where the stomach itself had a greenish cast because of contact with the nonviable cecum. In addition, the omentum in this region was somewhat greenish in the area that had been touched by the non-viable cecum. Penicillin in the amount of one half-million units was placed intraperitoneally along with one gram of streptomycin. Finally a small polyethylene tube adequate to pass through a #15 needle was placed in the left upper quadrant in the region of the greater indirect soiling from contact. There had been no tears in this necrotic bowel so I believe there was no direct soiling. The peritoneal cavity was then closed in layers with interrupted 3-0 silk sutures doubled in two places near the umbilicus, washing the wound after completion of closure. The subcutaneous tissues were approximated with catgut and the skin with 4-0 silk. The patient received several more bottles of blood on the table. Her blood pressure at the conclusion of this operation was slightly over 100, and her pulse was 120."

The entire resected specimen after emptying, weighed 535 gm. It was black in color, foul-smelling and greatly dilated. Microscopic examination of the resected colon revealed complete necrosis with extensive hemorrhage. The ileum was also necrotic and the wall of the appendix showed extensive necrosis.

Postoperatively the patient was at once improved but remained in serious condition for several days. By March 22 her temperature had returned to normal and remained so thereafter. She had received 400,000 units of penicillin four times daily, 0.5 gm. streptomycin twice daily, intramuscularly. Despite this, on March 24 there was definite evidence of a left subphrenic inflammation with a small pleural effusion. Paracentesis yielded 350 cc. of straw-colored sterile fluid. It is interesting that with this relatively minor bout of inflammation her leukocyte count rose to 11,100 per cu. mm. with 95 per cent neutrophils, while with the almost fatal gangrene of the cecum it was normal. Recovery from now on was gradual but steady and the patient was allowed to go home on April 10, 1954.

She was next seen by one of us (R. S.) on May 18, 1954, progressing very satisfactorily. The urinary porphyrins were again determined. (Table 1.) The fecal porphyrins were determined over a four-day period, May 16 to May 20, 1954. The fecal coproporphyrin was 46,000 μg./day (upper limit of normal 1,450), and the uroporphyrin 12,000 μg/day (upper limit of normal probably not > 200). These very high values in an early period of remission after the acute attack are of much interest especially as they were observed a year in advance of the appearance of any cutaneous lesions. The patient was not seen again until August 30, 1955, when she was asked to return for reexamination (C. J. W.). Her general condition was excellent. There were no complaints and no abnormal findings except some small whitish slightly roughened scars on the hands, arms and feet. Asked about these she said that they had started as "water blisters" during the last summer (1955), that she had never had anything like it before. There was nothing to indicate that the lesions were related to trauma and heat, and the patient was not aware of any photosensitivity, although a relation to light was of course suggested by the distribution of the blisters and their first appearance in the summer time. There was no pigmentation. The liver and spleen were not palpable. The urinary porphyrins were again recorded. (Table 1.)

TABLE 1
PORPHYRIN AND PORPHOBILINOGEN EXCRETION IN PATIENT S. F.

Date	Urine Porphobilinogen (units/24 hr. or qualitative results on single sample)	Copro-porphyrin (μg./24 hr.)	Uro-porphyrin (μg./24 hr.)
3/15/54	3+	.....	.....
3/16/54	3+	328 γ%	1760 γ%
3/17/54	38	2088	8208
3/18/54	9	2969	10773
3/19/54	6.1	3528	6347
3/22/54	0	4500	1600
3/24/54	0	3656	1213
3/25/54	+	1200	5160
3/26/54	0.7 u%	1313 γ%	345 γ%
3/28/54	0	3625	1050
3/30/54	0	2640	660
4/1/54	0	4810	1066
4/5/54	0	2903	753
4/7/54	0	3000	691
4/9/54	0	3243	925
4/10/54	0	3200	1120
5/18/54	+*	2280	1330
8/30/55	11	1625	5375

* Only + on concentration. Fifty cc. of urine adjusted to pH 8.0–9.0 with Na_2CO_3, mixed with 300 cc. acetone and 1 gm. of calcium acetate. The precipitate is collected and dissolved in a few cc. of water which is then mixed with an equal volume of Ehrlich's reagent. The color, absorption spectrum and $CHCl_3$ solubility of any aldehyde compound which is formed is noted, the latter after addition of an equal volume of saturated aqueous sodium acetate solution.

The patient agreed to have samples of urine sent in from as many of the immediate members of her family as possible. These data are given in Table II. Although none of the family members listed in Table II had known symptoms of porphyria, it is evident that at least one (A. Q.) has the disease in latent form.

TABLE II
URINE PORPHYRIN DATA ON SINGLE SAMPLES SENT IN FROM RELATIVES OF PATIENT S. F.

Initials	Relation	Age	Copro-porphyrin (γ/100 cc.)	Uro-porphyrin (γ/100 cc.)	Porpho-bilinogen
J. F.	Daughter	16	17.0	0.5	Negative
D. F.	Son	11	6.0	0.13	Negative
M. F.	Son	25	27.0	1.1	Negative
A. Q.	Sister	54	16.0	34.0	+ (weak)
A. L.	Daughter	20	8.5	1.7	Negative
L. F.	Son	5	8.0	0.4	Negative
R. F.	Son	23	44.0	1.5	Negative

The patient was last seen on February 27, 1956. She was feeling quite well and there had been no complaints and no further skin lesions since last summer. Liver function studies made at this time revealed the following: bromsulphthalein, 25 per cent retention at 45 minutes after 5 mg./kg.; serum bilirubin, prompt direct (1 minute) 0.1 mg./100 cc., total 0.4 mg./100 cc.; cephalin flocculation test, 3+ in twenty-four hours; thymol turbidity, 4 units.

STUDIES OF THE URINARY PORPHOBILINOGEN AND PORPHYRINS

The porphobilinogen or pyrrole compound responsible for the Ehrlich aldehyde reaction consistently behaved in an atypical fashion, as compared with ordinary porphobilinogen as crystallized by Westall [*3*], which has well defined chemical characteristics. The Ehrlich reaction became much more intense after addition of sodium acetate solution to Congo Red-negative reaction; while with ordinary porphobilinogen most of the color intensity develops immediately after addition of the Ehrlich reagent [*4*]. The α and β absorption bands of the aldehyde compound at maximum, 566 and 530 mμ., respectively, were not as sharply separated as with the Westall porphobilinogen. The aldehyde compound was not extracted by $CHCl_3$ but was completely extracted by butyl alcohol, this latter behavior being quite different from ordinary porphobilinogen [*5*]. Attempts to concentrate the present compound by Westall's method [*3*] were unsuccessful; it was obviously more labile to the mercury and H_2S treatment. Repeated attempts to convert the present Ehrlich reacting compound to porphyrin by heating, were inconclusive. (Table III.) It is well recognized, however, that under certain conditions even the Westall porphobilinogen may not be converted to porphyrin by heat, thus the significance of the data is not clear [*4*].

TABLE III
EFFECT OF HEAT ON URINE PORPHYRIN CONCENTRATION

Urine Adjusted to pH 4.0	Copro-porphyrin (μg./100 cc.)	Uro-porphyrin (μg./100 cc.)
Before heating	115	1080
After Δ at 80°C., 20 min.	210	1080
Before heating	2088	8208
After Δ 80°C., 20 min.	2016	8266
Before heating	328	1760
After Δ 80°C., 20 min.	370	2000

Extraction of the native urine at pH 4.0 with petroleum ether failed to remove any of the Ehrlich reagent reacting compound, thus excluding the presence of any of the urobilinogen group [*6*]. It was of interest, however, that an orange, urobilin-like compound formed during the Ehrlich reaction and was extracted by $CHCl_3$, leaving the Ehrlich aldehyde compound in the aqueous phase. The orange urobilinoid or atypical porphobilin, as the case may be, exhibited an absorption band maximum at 490 mμ., but on addition of alcoholic zinc acetate to the $CHCl_3$ solution a pink color appeared without green fluorescence.

Isolations and chromatographic studies of the urinary porphyrins were made on the urine samples. The first sample covered the period from admission on March 15 to operation on March 16; the second from noon on March 16 to 8 A.M. on March 17. The urine, collected at an alkaline pH (Na_2CO_3), was adjusted with acetic acid to pH 4.0 and, without heating, the total porphyrin was adsorbed on talc, then eluted and esterified with methyl alcohol, as previously described [*7*]. Further preparative work and $CaCO_3$ chromatography were performed in the usual manner [*7*]. Paper chromatography of uroporphyrin esters was performed according to the Falk-Benson method [*8*], and of the coproporphyrin esters and related porphyrins by the method of Chu-Green [*9*]. The

fluorescence quenching method for distinction of the coproporphyrin isomers [*10*] was also used.

The uroporphyrin from the first sample exhibited two poorly separated zones on the $CaCO_3$ column. The main (upper) zone, contained 505 μg. of porphyrin of which 205 μg. was obtained after recrystallizing four times. This melted at 264–267°C., α absorption band maximum at 626.7 type I > III by Falk-Benson chromatography. Unfortunately this compound was lost in decarboxylation. The mother liquor contained 300 μg., indicated by Falk-Benson chromatography to be I and III plus a small amount of 7-COOH porphyrin. On decarboxylation the total coproporphyrin was 52 per cent III by fluorescence quenching, equal quantities of I and III by the Chu-Green method.

The coproporphyrin fraction from the first sample also subdivided into two zones on repeated $CaCO_3$ chromatography. The upper of these had an α absorption band in $CHCl_3$ maximum at 625.9 mμ. and on Falk-Benson paper chromatography exhibited spots indicating 6, 5, 4 and 3-COOH porphyrins, in addition to a trace of coproporphyrin. The lower zone had an α absorption band at 621.7 and appeared to be nearly all coproporphyrin. The Chu-Green and fluorescence quenching methods both indicated mainly type III isomer.

The results obtained with the second urine sample were essentially the same and need not be repeated in any detail. Again the Waldenström uroporphyrin complex was composed about equally of types I and III, and a small amount of the type III, 7-COOH porphyrin was observed. The native coproporphyrin was a mixture of I and III, the latter predominating. Very small amounts of 6, 5 and 3-COOH porphyrins were also noted.

COMMENTS

This case is worthy of record mainly because of the volvulus which appeared to be secondary to the porphyria and which nearly caused the patient's death. The diagnosis of porphyria and the knowledge that in this disease segments of colon are often greatly distended was unquestionably misleading and caused delay in operation. The absence of fever and the normal leukocyte count on admission, when there is little doubt, in retrospect, that the volvulus was already well established, were also confusing. The shock-like state on admission was initially assumed to be due to depletion of water and electrolyte, as often seen in acute porphyria, although it appears now that insufficient attention was paid to the normal serum sodium and potassium values observed soon after admission.

Fortunately, mechanical complications such as volvulus, intussusception and strangulation of bowel, secondary to porphyria, appear to be very rare. Only one other somewhat similar case has come to our attention. This was in one of identical twin brothers studied by W. W. Reynolds* [*11*]. The twin seen by Dr. Reynolds had had repeated typical attacks of acute porphyria but it was his brother, studied in the United States, who in 1945 noted dark urine and in 1946 had 30 inches of gangrenous small bowel resected, at which time red urine was again observed. According to Dr. Reynolds this patient succumbed to another attack of porphyria in 1953.

The present case is also of considerable interest from the standpoint of classification. Up to and including the episode of volvulus the only designation which would seem justified is that of acute porphyria. At the time of the last visit, however, the patient had only very minor skin lesions and otherwise latent porphyria, best described now as the cutanea tarda type. Rimington and co-workers [*12*] believe that the cutanea tarda and the acute types represent independent diseases, although the experience in this laboratory [*13*] and the recent genealogic studies of Dean and Barnes [*14*] indicate that they are simply variants of one fundamental abnormality. Calvert and Rimington [*12c*] believe that a high fecal porphyrin excretion in remission serves to distinguish porphyria cutanea tarda as a disease entity fundamentally different from the acute type. The present case, however, illustrates the difficulty that this view poses. It seems more reasonable to assume that the difference is only one of a functional stage in the liver, such that in acute porphyria the liver cell releases much of the porphobilinogen and converts but little of it to porphyrin, while in the cutanea tarda type (or sequel, as in the present case) much or all of it is converted to porphyrin by the liver. As noted in an earlier paper [*13*] evidence for such a variation may be obtained in liver biopsies taken at widely separated times in the same case.

* We are indebted to Captain Reynolds for the information about these cases. Dr. Reynolds reported them at a meeting at the U.S. Army 320th General Hospital, Landstuhl, Germany, Sept., 1954, and has kindly permitted this reference to his report.

The view might be taken with respect to the present case that the volvulus and the porphyria were coincidental. Against this, however, is the fact that the patient had only moderate abdominal pain together with red urine for about ten days before the acute manifestations of volvulus developed. In addition there was considerable albeit atypical porphobilinogen in the urine which disappeared within a few days after operation. It is noteworthy, too, that the first symptom was vomiting. This preceded the onset of abdominal pain which for the first three days after its appearance was suprapubic in character. It is also of considerable interest that the exacerbation of porphyria which initiated the volvulus, if one accepts this sequence, promptly abated after operation. Of course it is well known that remission in acute porphyria often occurs spontaneously and rapidly, and that it may occur shortly after ACTH or cortisone therapy, although this is not consistently true [*2*]. All in all it is believed that this case is best classified as a "mixed" or "combined" type of hepatic porphyria, on the basis of our recent classification [*2,13*].

In view of the marked disturbances in motor function of the bowel in porphyria it is somewhat surprising that volvulus has not been observed more frequently. From the practical point of view the possibility should be considered in any case of porphyria showing increasing bowel distention and inflammatory signs, especially if accompanied by a weakening pulse not readily explained by dehydration and electrolyte depletion.

SUMMARY

An unusual case of combined hepatic porphyria is described in which volvulus of the cecum nearly resulted in death. It is believed that the volvulus was secondary to disturbed motor function of the bowel caused by the porphyria. Operation resulted in complete remission. Subsequently mild "cutanea tarda" symptoms developed in this patient and the excessive porphyrin excretion persists two years after the episode of volvulus.

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A Case of Coexistent Non-meningitic Cryptococcosis and Boeck's Sarcoid*

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THE coexistence of cryptococcosis and sarcoidosis was earlier described by Collins [*5*], Fisher [*8*] and Gandy [*11*] and was represented in about 0.8 per cent of the 241 cases of cryptococcosis reviewed by Collins et al. [*6*]. However, as far as can be determined, the case presented herein, mentioned also by Littman and Zimmerman [*18*], brings the total number of such cases reported in the literature to no more than five.

The following is a presentation of the case report; a description of the laboratory measures employed to establish the presence of the two diseases; and; finally, a résumé of therapeutic trials with 2-hydroxystilbamidine, mycostatin® and amphotericin B, with two of which, protective studies in mice experimentally infected with the strain of Cryptococcus neoformans isolated from the patient were also carried out.

CASE REPORT

A twenty-two year old Negro airman, stationed in the Far East, was well until January, 1954, when he noted tightness in the chest accompanied by expiratory and inspiratory wheezing. This was followed by cervical adenopathy six months prior to admission; malaise, anorexia and a 20 pound weight loss two months before admission and; finally, right chest pain, which led to his first hospitalization. At that time the only physical findings were numerous cervical, epitrochlear and inguinal nodes, 1 to 3 cm. in diameter, and bilateral expiratory wheezing. Chest films revealed a widened mediastinum and bilateral hilar enlargement, particularly on the right. There was a moderately extensive bilateral pulmonary infiltrate. An osteolytic lesion on the right iliac crest was discovered on the pelvic films. Cervical and epitrochlear node biopsies revealed granulomas compatible with Boeck's sarcoid. Special stains disclosed no fungi or acid-fast bacilli. A Turkel needle biopsy of the right iliac crest lesion revealed degenerated bone and connective tissue. An elevated serum globulin (4.7 gm. per cent), total protein (10.1 gm. per cent) and alkaline phosphatase (7.2 Bodansky units) were found. Therapy with oral cortisone was followed by symptomatic improvement and regression of the lymphadenopathy. (Fig. 1.)

The patient was transferred to this hospital on March 2, 1955. On admission he complained of low back pain radiating to the left knee. Physical examination revealed only a few small right epitrochlear nodes and the lungs were clear. The low back pain radiating to the left knee, as well as a low grade temperature, were thought to represent reactivation of Boeck's sarcoid with possible impingement on the nerve roots between the fifth lumbar and the first sacral vertebrae. Cortisone was reinstituted at a maintenance dose between 50 to 100 mg. daily in divided doses. Gradually, a tender discolored swelling developed over the left hip. Attempts to aspirate the lesion with No. 18 needles were not successful, and an exploration§ of the left hip was made on June 24, 1955. At that time one-half pint of thick, dirty-brown, creamy pus was removed from an abscess cavity underlying the gluteus maximus. The abscess extended from the sacroiliac joint superiorly to the mid-thigh inferiorly. A biopsy of the abscess wall and 5 cc. of pus were obtained for study. Following surgery, complete bed rest and prophylactic intramuscular penicillin and streptomycin were instituted. Cortisone dosage was gradually reduced and finally discontinued.

Laboratory data: The laboratory data obtained on

§ Surgery was performed by Captain M. Altchek, USAF (MC) and Major J. Anderson, USAF (MC).

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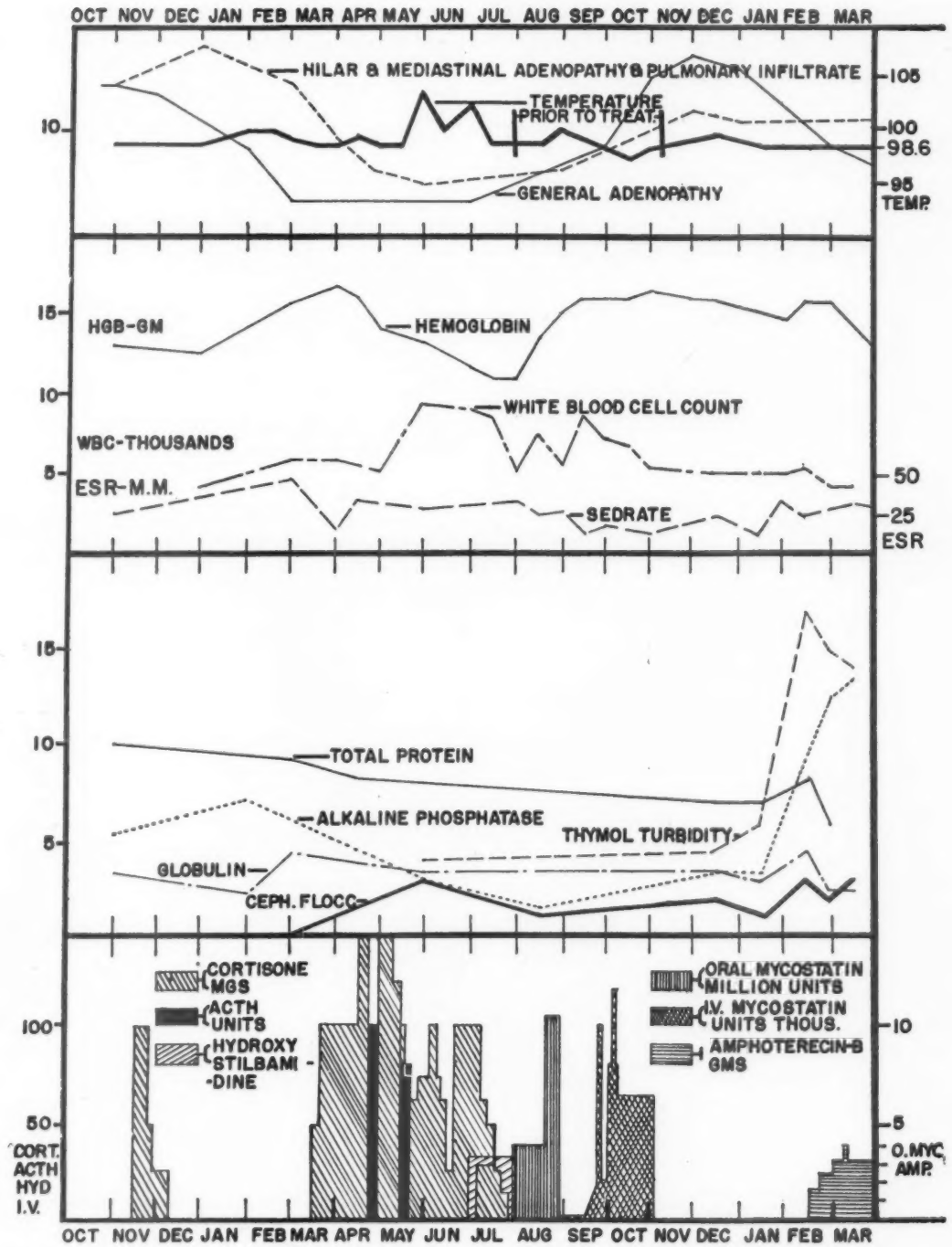

FIG. 1. Graphic relationship of the laboratory data, fever, adenopathy and therapy. Waxing and waning of the generalized adenopathy was associated with liver profile changes. The temperatures between brackets were taken prior to each individual dose of mycostatin to avoid confusion with the resulting febrile reaction to that medication.

admission (March 2, 1955) were as follows: hemoglobin, 16.6 gm. per cent; white blood cells, 5,700 per cu. mm.; differential blood count, normal; hematocrit, 47 per cent. Urinalysis and routine cardiolipin microflocculation test were negative. Blood chemistry: cephalin flocculation test, negative; thymol turbidity test, 7 units; total protein, 9.3 gm. per cent; albumin, 4.8 gm. per cent; globulin, 4.5 gm. per cent; bilirubin, 1 mg. (Serial liver profiles and blood counts are shown in Figure 1.)

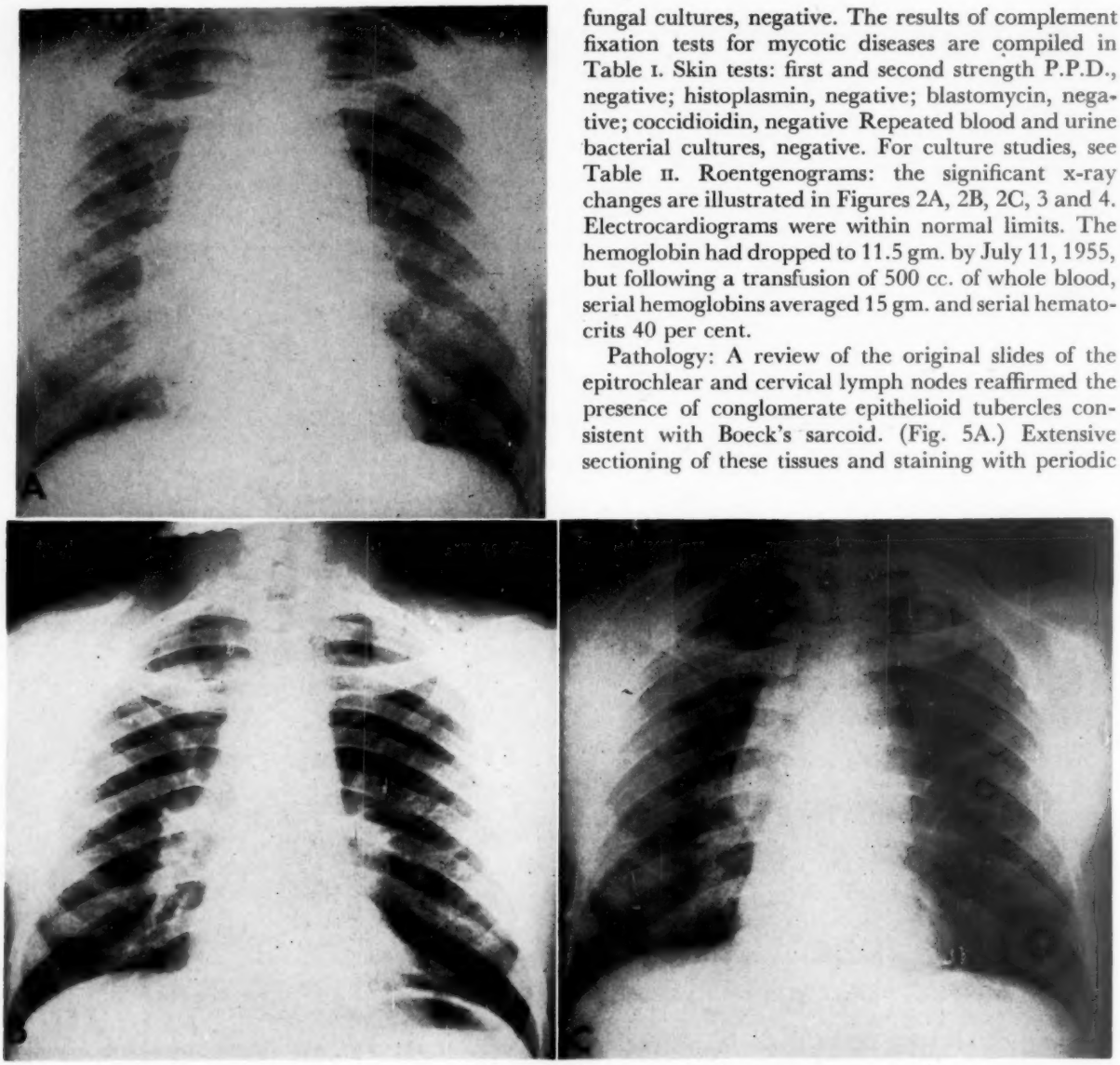

FIG. 2. The marked reduction in the extent of the parenchymal infiltrate and the size of the hilum and mediastinum which occurred during steroid therapy are shown in B (May, 1955). C, (March, 1946) demonstrates the recurrence of these findings following the discontinuation of cortisone and ACTH, but not to the extent noted in A (December, 1954).

fungal cultures, negative. The results of complement fixation tests for mycotic diseases are compiled in Table I. Skin tests: first and second strength P.P.D., negative; histoplasmin, negative; blastomycin, negative; coccidioidin, negative Repeated blood and urine bacterial cultures, negative. For culture studies, see Table II. Roentgenograms: the significant x-ray changes are illustrated in Figures 2A, 2B, 2C, 3 and 4. Electrocardiograms were within normal limits. The hemoglobin had dropped to 11.5 gm. by July 11, 1955, but following a transfusion of 500 cc. of whole blood, serial hemoglobins averaged 15 gm. and serial hematocrits 40 per cent.

Pathology: A review of the original slides of the epitrochlear and cervical lymph nodes reaffirmed the presence of conglomerate epithelioid tubercles consistent with Boeck's sarcoid. (Fig. 5A.) Extensive sectioning of these tissues and staining with periodic acid-Schiff, mucicarmine and Gomori stains revealed no structures morphologically suggestive of any of the mycotic agents.* Scrapings of the lymph nodes stained with India ink were also negative for C. neoformans.

Subsequent laboratory data were as follows: Blood chemistry: fasting blood sugars, 78 to 105 mg. per cent; cholesterol, 178 to 250 mg. per cent; cholesterol esters, 65 to 73 per cent. The results of lumbar punctures were as follows: June 8, 1955, initial pressure, 8.5 cm. of water; final pressure, 7 cm. of water after removal of 10 ml. of clear fluid; cells, none; protein, 30 mg. per cent; sugar, 81 mg. per cent; globulin, negative. July 28, 1955, initial pressure, 12 cm. of water; final pressure, 8 cm. of water, after removal of 10 ml. of clear fluid; 4 mononuclear cells; protein, 31 mg. per cent; sugar, 72 mg. per cent; chloride, 112 mg. per cent; globulin, negative; bacterial and

In contrast, the hematoxylin and eosin stained sections of the excised abscess wall showed a subacute inflammatory reaction composed of large mononuclear cells with vesicular cytoplasm, lymphocytes

* We are indebted to Drs. Chapman H. Binford and Lorenz E. Zimmerman, Armed Forces Institute of Pathology, for their assistance and cooperation.

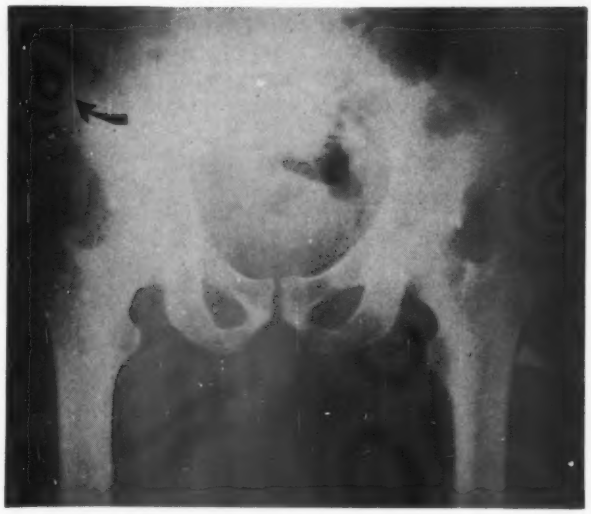

FIG. 3. The irregular osteolytic lesion above the right iliac crest has no overlying cortex. The greater trochanter of the left femur shows some irregularity and haziness of the cortex and the trabecular pattern, but no definite lesion is present. A transient calcific line developed over the lateral aspect of the left greater trochanter but disappeared on follow-up films.

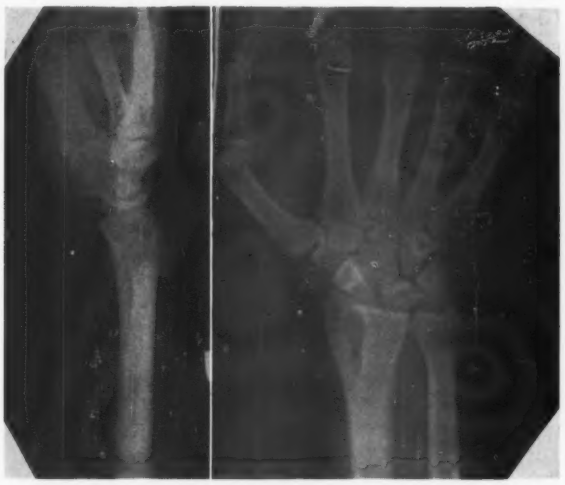

FIG. 4. An elliptic, double-chambered, subcortical, osteolytic lesion is present on the dorsal aspect of the distal end of the right radius. This lesion was not noted on films prior to January 10, 1956.

and a few neutrophils. (Fig. 5B.) Moreover, there was a suggestion of the presence of intracytoplasmic bodies in a number of the large histiocytic cells (Fig. 5C) which with the Gomori methenamine stain were clearly demonstrated as C. neoformans. (Fig. 5D.)

EXPERIMENTAL STUDIES

As shown in Table I, the specimens of serums from the patient fixed complement in low but equivocal titers (1:8) with each of two histoplasma antigens [*13*] and to even higher levels (1:16–1:64) with a yeast phase antigen of Blastomyces dermatitidis. The collodion agglutination tests with histoplasmin [*22*] were uniformly negative. Single specimens obtained from three persons in the patient's immediate family were also negative in both types of serologic tests.

In the cultural and mouse inoculation studies (Table II), C. neoformans was isolated from pus from the patient's hip lesion on two separate occasions. Three additional specimens from this source and specimens of sputum, urine and spinal fluid failed to yield this organism or any of the other pathogenic mycotic agents.

Mice infected with the strain of C. neoformans isolated from this patient and treated with a total dosage of 5.0 mg. (250 mg./kg.) mycostatin (Lot No. HA-337-A) survived for longer periods of time than those that were untreated. Specifically, the calculated per cent protection* was 80, 53.4 and 26.7 on the fourteenth, twenty-first and twenty-eighth day, respectively, thus indicating that the drug might be effective in treating the patient from whom this particular strain was recovered. Similar studies with amphotericin B using a total dosage of 0.25 mg. (12.5 mg./kg.) yielded a calculated per cent protection of 95.9 74.5, 56.5 and 45, at seven, fourteen, twenty-one and twenty-eight days, respectively. This suggested that amphotericin B might be even more effective in treating cryptococcosis in humans.

TABLE I
SEROLOGY

Specimen	Complement Fixation			Collodion Agglutination
	Histoplasma (Yeast Phase Antigen)	Blastomyces (Yeast Phase Antigen)	Coccidioidin	Histoplasmin
Patient's serum:				
7/6/55	1:8	1:16	Negative	Negative
7/25/55	1:8	1:32	Negative	Negative
8/31/55	.....	1:64	Negative	Negative
Aunt's serum	Negative	Negative	Negative	Negative
Sister's serum	Negative	Negative	Negative	Negative
Father's serum	Negative	Negative	Negative	Negative

* Calculated per cent protection =

$$100 - \left(\frac{\%\ \text{deaths treated, infected mice}}{\%\ \text{deaths untreated, infected mice}} \times 100 \right)$$

TABLE II

SUMMARY OF FINDINGS IN LABORATORY STUDIES ON CLINICAL MATERIALS

Date	Specimen	Direct Examination			Petragnani Medium	Culture				Animal Inoculation		Organism
		Gram Strain	Acid-Fast	India Ink		Veal Infusion Agar		Sabouraud's Agar		Guinea Pig for Tubercle Bacilli	Mice for Fungi	
						Temperature (Room)	(37°C.)	Temperature (Room)	(37°C.)			
6/20/55	Spinal fluid	.....	.....	Negative	.....	Negative	Negative	Negative	Negative	.....	Negative	No pathogenic fungi
6/30/55	Pus from left hip abscess	Positive	Negative	Positive	Negative	Positive	Positive	Positive	Positive	Negative	Positive	C. neoformans
7/17/55	Pus from right iliac crest abscess	.....	.....	Positive	.....	Positive	Positive	Positive	Positive	.....	Positive	C. neoformans
7/27/55	Urine	Negative	Negative	Negative	.....	Negative	Negative	Negative	Negative	.....	Negative	No pathogenic fungi
7/27/55 8/2/55	Sputum	.....	.....	Negative	.....	Negative	Negative	Negative	Negative	.....	.....	No pathogenic fungi
9/1/55	Swab from left hip abscess	.....	.....	Positive	.....	Negative	Negative	Negative	Negative	.....	Negative	C. neoformans
9/26/55	Swab from left hip abscess	.....	.....	Negative	.....	Negative	Negative	Negative	Negative	.....	Negative	No pathogenic fungi
11/3/55	Epitrochlear lymph node	.....	.....	.....	.....	Negative	Negative	Negative	Negative	.....	Negative	No pathogenic fungi

Neither B. dermatitidis nor Histoplasma capsulatum was recovered from any of the clinical specimens in spite of intensive cultural and mouse inoculation studies. Nor were organisms morphologically suggestive of these two agents observed in histologic sections stained by the more recently developed technics. Although the CF titers obtained with blastomyces antigen especially were as high or higher than those demonstrated in many verified cases of blastomycosis or histoplasmosis, it should be emphasized that the mycotic antigens in current use cross react to a marked degree in serums from a number of different systemic mycotic diseases, as has been pointed out repeatedly in earlier reports [*1*]. In view of these two factors, therefore, it is highly unlikely that more than one mycotic organism was involved in this case.

TREATMENT AND MATERIALS

Treatment with 2-hydroxystilbamidine was started on June 30, 1955, and continued until August 1, 1955, as illustrated in Figure 1. The drug was administered intravenously in daily doses of 225 mg. dissolved in 200 ml. of 5 per cent dextrose in water. To prevent untoward toxic reactions, only freshly prepared solutions were employed and these were covered with two ordinary shopping bags during the period of administration in a darkened room. Nevertheless, slight nausea and anorexia ensued.

At this juncture the diagnosis of cryptococcosis was definitely established and the therapeutic agent was changed to mycostatin. This antibiotic was at first administered orally and, as shown in Figure 1, the patient eventually received a daily dose of 10.5 million units given in divided doses every two to three hours for a period of twenty-two days (August 1 to 21, 1955). Slight nausea was noted.

On August 22, 1955, however, an intravenous preparation of mycostatin (Lot No. ST 695-714/14–3E) was made available and used until September 28, 1955. Chills and temperature elevations up to 103°F. followed doses greater than 1,000 units dissolved in 200 to 1,000 cc. of 5 per cent dextrose in water in spite of the use of salicylates and chlor-trimeton® during and prior

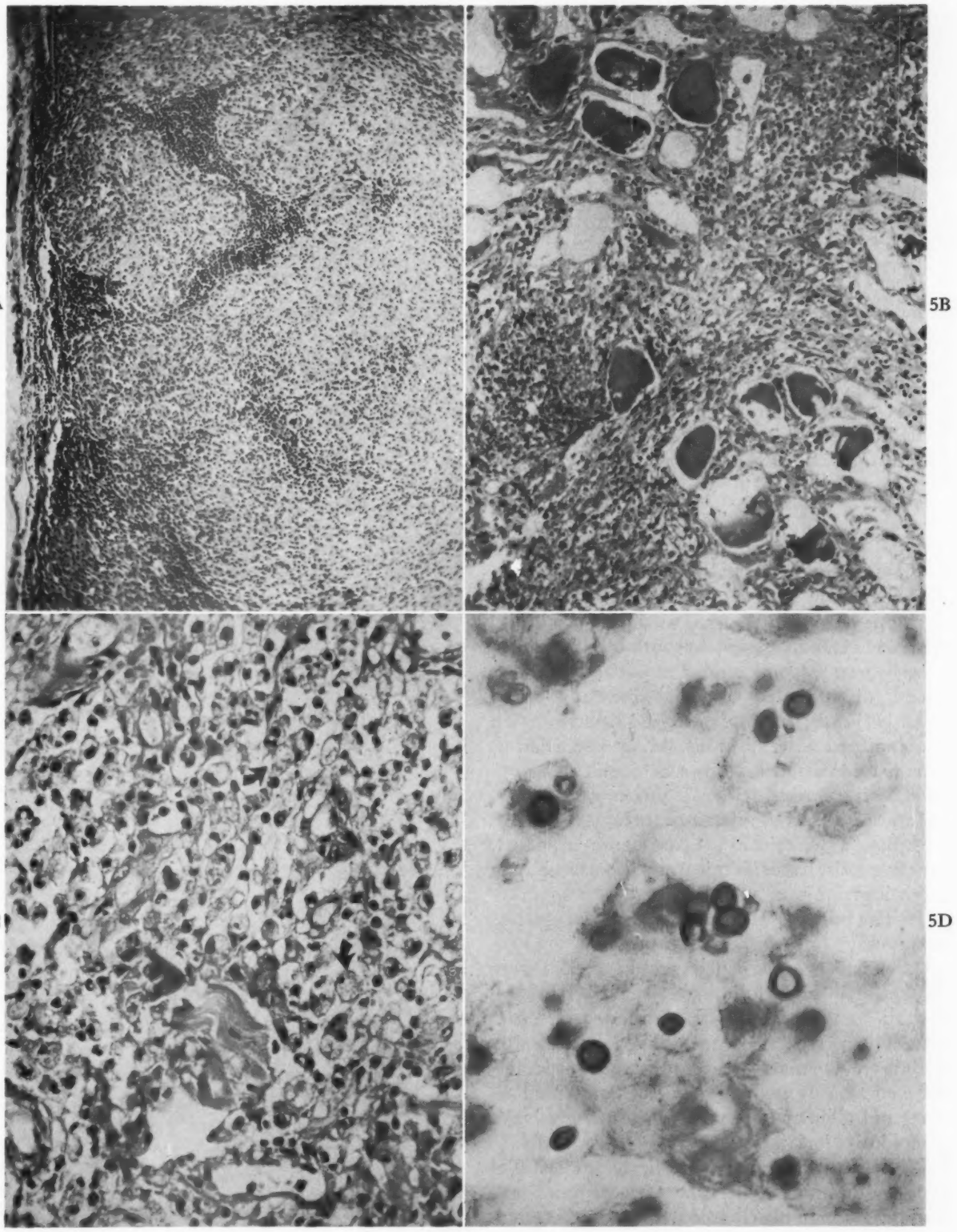

FIG. 5. A, an epitrochlear lymph node showing typical epithelioid tubercles consistent with Boeck's sarcoid. Hematoxylin and eosin stain; original magnification, × 75. B, the excised abscess wall from the left hip revealing skeletal muscle fibers and a subacute, inflammatory reaction. Hematoxylin and eosin stain; original magnification, × 125. C, large mononuclear cells with vesicular cytoplasm, lymphocytes and neutrophils with a suggestion of the presence of intracytoplasmic bodies in a number of the large histiocytic cells (arrows). Hematoxylin and eosin stain; original magnification, × 310. D, Cryptococcus neoformans organisms in excised abscess wall. Gomori methenamine silver stain; original magnification, × 1,440.

to each dose.* Finally, on August 29, 1955, treatment with a recrystallized intravenous mycostatin (Lot No. 4) was started and continued until November 3, 1955. Daily doses of 66,666 units of this preparation were well tolerated and without side effects.

Therapy with amphotericin B [*26*] was initiated on February 4, 1956. When oral dosages of 400 mg. every six hours produced no untoward effects, the total dosage was gradually increased. Dosages of 600 mg. every six hours evoked an episode of diarrhea which subsided spontaneously in a few hours and did not recur. After three days on a dose of 1 gm. every six hours the patient vomited following each dosage. The drug was then discontinued and after twenty-four hours reinstated at 3.2 gm. daily. Later increase to a total dosage of 5 gm. produced no side effects. Continued therapy is indicated because of the persisting radial lesion.

COMMENTS

The finding of Boeck's sarcoid in combination with one of the systemic mycotic infections does not appear to be too unusual. Hiatt et al. [*12*] reported a case in association with blastomycosis, Ellis [*7*], a second one complicated by arrested, disseminated coccidioidomycosis, Israel et al. [*14*] described the entity in a patient with disseminated histoplasmosis. As noted earlier, at least five cases of coexisting sarcoidosis and cryptococcosis are recorded.

In addition to the tissue pathology consistent with Boeck's sarcoid in the case herein reported, the diagnosis of sarcoidosis was supported by the following:

1. The patient was a Negro man, twenty-two years of age [*8,10,16,17*].

2. Chemistries revealed an elevated serum total protein and globulin, and positive thymol turbidity and cephalin flocculation tests [*15,16*].

3. The presence of generalized adenopathy with involvement of preauricular, postauricular, submental, submaxillary, epitrochlear, mediastinal and hilar nodes is particularly suggestive of sarcoidosis [*19,28*].

4. During the course of cortisone and ACTH therapy there was regression of the adenopathy and reversion of the chemical findings to normal. When the steroids were discontinued, these findings recurred.

5. Careful cultural and histologic studies including the earlier lymph nodes ruled out the presence of C. neoformans in all three nodes studied.

6. Negative first and second strength P. P. D. reactions were obtained on repeated occasions [*15*].

7. A Nickerson-Kveim test performed according to the procedure delineated by Siltzbach and Ehrlich [*24*] was positive. There is still controversy regarding the diagnostic value of this test. Siltzbach and Ehrlich [*24*] reviewed the reports by Kveim, Putkonen, Danbolt and Lamholt in which 3 to 6 per cent false positive Nickerson-Kveim reactions were found. Siltzbach and Ehrlich [*24*] reported 85 to 86 per cent histologically positive responses in "biopsy confirmed" and strongly suspected cases of sarcoid, and only 4 per cent false positive tests. Israel and Sones [*15*], on the other hand, tested eighty-one subjects of whom twenty-eight had sarcoidosis, thirty-three had tuberculosis and twenty were controls. A total of 114 Kveim tests were performed. Only 21.1 per cent positive responses were found in the subjects with sarcoidosis, while 42.4 per cent of the tuberculous patients and 8.3 per cent of the controls gave positive tests.

In spite of the presence of two abscesses and an osteolytic lesion of the distal end of the right radius, there was no evidence of meningeal involvement as determined by lumbar puncture or extensive cultural studies during the eighteen-month period of clinical observation. The nonmeningitic type of cryptococcosis comprised 20 per cent of the cases reviewed by Carton and Mount [*4*] and was described in those reported by Collins et al. [*6*]. Of the 241 cases of cryptococcosis reviewed by the latter, 20 per cent had pathologic changes in the reticuloendothelial system, although only two cases in the series were definitely proved to be combined with sarcoidosis. Three, which initially were considered as coexisting infections of cryptococcosis and sarcoidosis, on further study were ascribed to the etiologic agent, C. neoformans, alone.

As with other deep mycotic infections, the treatment of cryptococcosis by a variety of therapeutic measures and drugs has been unrewarding, and cures or improvement in nearly all cases is equivocal or absent. Mosberg and Arnold [*21*], who reviewed the treatments used

* Intravenous preparations of mycostatin were dissolved in a special diluent furnished by E. R. Squibb & Sons. This diluent when mixed with 5 per cent dextrose in water produced a mild febrile reaction and chills.

in a series of cases, found no one procedure which produced anything but equivocal improvement in the patient, although sulfonamides, penicillin, potassium iodide, arsenicals, intravenous alcohol, antigens of C. neoformans and deep x-ray, surgical excision and fever therapy all were variously employed. Freeman [*9*], as early as 1931, suggested that the chronic nature and usually fatal outcome of the disease was due to the lack of inflammatory response. It is perhaps this very chronicity, with subsequent variation in the longevity of each individual case, which makes the results of therapeutic measures difficult to evaluate. Of the group of fourteen cases of central nervous system cryptococcosis analyzed by Carton and Mount [*4*] in only the one reported by Marshall and Teed did recovery appear to be complete.

Nevertheless, the search for therapeutic agents has continued, and in 1953 Carton and Liebig [*3*] reported that acti-dione® and polymyxin B combined possessed greater inhibitory activity against the growth of C. neoformans *in vitro* than any of the other twenty-seven drugs employed in their study. Acti-dione has subsequently been tried in human cases.

The use of diamidines for treatment in the deep mycoses was introduced in 1952 by Schoenbach [*23*] who used stilbamidine with marked success in cases of North American blastomycosis. Even greater success was achieved by Snapper and McVay [*25*] whose cases were treated with 2-hydroxystilbamidine. In cryptococcosis, however, results were again equivocal. Whitehill [*27*] reported a dramatic response in a sixteen year old Negro girl with a disseminated, nonmeningeal infection following administration of stilbamidine, while Miller [*20*] noted only transitory improvement in three ultimately fatal cases in which the patients received this drug.

Therapy with 2-hydroxystilbamidine was initiated in the case reported herein when early studies indicated that the disease was North American blastomycosis, rather than cryptococcosis. Following a total dosage of 7.4 gm. drainage from the left hip abscess was diminished and the subjective over-all state of the patient improved. Nevertheless, while the patient was still under treatment a new abscess formed at the site of the previously noted right iliac crest lesion and C. neoformans organisms were continuously demonstrable in India ink preparations of the exudate from the left hip. For these reasons further therapy with 2-hydroxystilbamidine was discontinued.

Mycostatin, because of its promising protective activity in mice infected with C. neoformans [*2*], was next employed. Prolonged therapy with intravenous preparations of this drug was accompanied by complete healing of both hip lesions, although the initial lot used produced chills and high fever when dosages of more than 1,000 units were administered. Similar reactions have been observed in approximately 10 per cent of all patients undergoing therapy with this preparation.* The second lot of drug, which was recrystallized, was well tolerated in doses up to approximately 66,666 units daily. Following sixty-six days of continuous therapy with these intravenous preparations there was no evidence of further activity, and therapy was stopped.

One month following the cessation of treatment with mycostatin massive generalized adenopathy recurred and after six weeks an osteolytic lesion appeared in the distal end of the right radius. The latter was exquisitely tender to the touch, discolored and swollen, and there was diminished range of motion of the right wrist. That there was a renewal of sarcoid activity was indicated not only by the recurrence of generalized adenopathy but by the changes in the "liver profile" and widening of the mediastinum. Nevertheless, antifungal therapy appeared to be mandatory to prevent further dissemination of the cryptococcosis. Since recrystallized mycostatin was no longer available,† therapy was started with the more recently developed and heretofore virtually untried antifungal antibiotic, amphotericin B. The oral administration of a total daily dosage of 5 gm. of this drug, along with supportive therapy consisting of salicylates and immobilization of the wrist, was accompanied by marked subjective improvement in the wrist. There was also evidence of new bone formation in the osteolytic right iliac crest lesion, with development of a definite trabecular pattern and overlying cortex. The radial bone lesion, however, is still present and unchanged.

At the present time there are still no signs of central nervous system involvement and no new bone lesions have been observed. The patient,

* Personal communication from Dr. Harvey Blank, Squibb Institute of Medical Research.

† Manufacture of *intravenous* mycostatin preparation was discontinued because of the severe side effects observed following its administration.

who is still hospitalized on convalescent status, complains of an occasional aching pain over the left hip after prolonged periods of standing or walking, but otherwise carries on his normal activities. In view of the abnormal liver profile and mediastinum, as well as the generalized adenopathy, it is assumed that some sarcoid activity still persists.

SUMMARY

A case of coexistent non-meningitic cryptococcosis and Boeck's sarcoid is presented, together with pertinent laboratory tests and experimental therapeutic trials with 2-hydroxystilbamidine, mycostatin and amphotericin B.

Acknowledgments: We are grateful to E. R. Squibb and Sons for providing the mycostatin and amphotericin B used in this case, and also for the kind cooperation of Drs. Blank and G. Hildick-Smith.

The illustrations in Figure 5 were made by the Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington 12, D. C.

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A Study of Host-Parasite Relationship in Loa Loa*

A Case Report

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PATHOGENIC filarial infections in man have been confined principally to four species of worms (Wuchereria bancrofti and malayi, Onchocerca volvulus and Loa loa) [*1–12*]. Despite considerable knowledge of these parasites, there has been surprisingly little understanding of the exact manner whereby these species exert their pathogenic effect.

Hypersensitivity to parasitic antigen has been suggested as important in the mechanism of filarial infection [*13–22*]. Coordinated objective laboratory and clinical data in support of this concept thus far have been inadequate. In the present study further data favoring the concept of hypersensitivity have been made available by the study of a case of loiasis of twelve years' standing. A detailed study of this case was undertaken in an attempt to (1) determine the host response to prolonged untreated filarial infection and (2) measure by clinical and laboratory methods any changes in this response with institution of therapy, with particular reference to studies of visceral functions and the serologic reflections thereof, and (3) effect a clinical improvement and possible remission.

CASE REPORT

The patient was a twenty year old white female college student who was admitted to the George Washington University Hospital on November 3, 1952, with a history of first exposure to Loa loa infection in 1940.

The first manifestations were noted approximately one year later, while in Gabon, French Equatorial Africa, a highly endemic area for loiasis [*23*]. These were complaints of an intermittent crawling sensation in varied skin areas associated with itching and occasional low grade fever. Six months to one year later the patient noticed wormlike forms beneath the skin on the extensor surface of her forearm; these forms had continued to be active in different areas of her body on varied occasions. She described the worms as having the appearance of a reddish, irregular, wavy line about ½ to 1 inch in length, and the "size of a pin" in diameter, remaining visible from a period of a few seconds to eight to twelve hours. One episode of a worm in the subconjunctival tissues had occurred, the migration taking three to five minutes. This was associated with itching, burning and increased lacrimation. The patient stated that she was able to localize many of the adult worms by being able to feel them move in the deep layers of the skin in various parts of her body, although frequently no objective signs would be visible.

After four years in Gabon, Africa, the patient returned to the United States (Florida), apparently in fairly good health except for feeling run-down and for occasional symptoms of subcutaneous activity of adult worms. During the next seven years, with increasing frequency, she noted intermittent swellings which appeared in many parts of her body and were accompanied by malaise. These Calabar swellings were described as tissue swellings, usually non-painful, occurring most often about a joint and lasting for variable periods of time up to one day. The largest of these swellings was about 4 inches in diameter.

After seven years in Florida she moved to Indiana (1951) and was exposed for the first time to cold winters. From the time of this climatic change until the hospital admission in 1952 she had increased symptoms, almost to the point of incapacitation, with increased surface activity of worms, severe malaise, arthralgia, backache, neckache, vertigo, intolerance to the extremes of heat and cold, occasional night sweats, diurnal frontal headaches, diurnal listlessness, severe nocturnal restlessness, occasional somnambulance, talking in her sleep, and more recently abdominal pain of a variable and indistinct type accompanied by distention, flatulence, eructations and constipation.

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The abdominal symptoms persisted after an elective appendectomy in September, 1952. Premenstrual aggravation of all complaints was noted.

Physical examination at the time of admission revealed a well developed, well nourished white woman appearing listless but in no acute distress. Her temperature was 37°C., pulse 80, respirations 24, blood pressure 110/60, height 60½ inches and weight 115 pounds. No abnormalities of the skin were noted. Several small, discrete, non-tender lymph nodes were palpable in the neck. Examination of the chest was negative. The abdomen was slightly protuberant with no tenderness and no palpable masses or viscera. Peristalsis was slightly hyperactive. Rectal and pelvic examinations were normal. More complete studies later revealed bilateral congenital nephroptosis and left double ureter with a double renal pelvis. Generalized abdominal visceroptosis was also noted but was felt to be asymptomatic. Neurologic examination was negative.

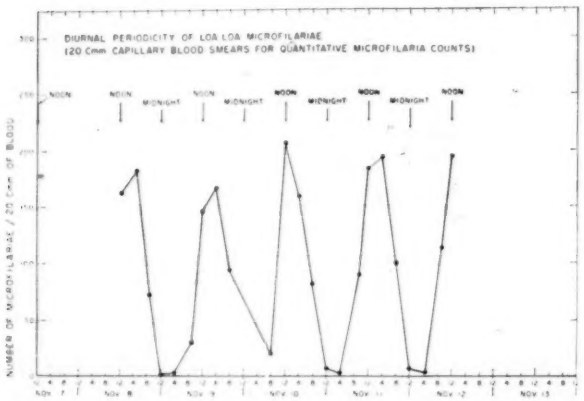

FIG. 1. Periodicity chart of microfilariae loa in the patient reported herein.

Laboratory studies on admission revealed a leukocyte count of 12,100 per cu. mm. with 9 per cent eosinophilia. The total eosinophil count was 1,729 per cu. mm. The hematocrit was 43 per cent and the sedimentation rate 25 mm. in one hour (Wintrobe, corrected). The gamma globulin was 10.5 units measured by the zinc sulfate technic [*24*]. The serum albumin was 3.8, serum globulin 3.4 gm. per cent. Liver function tests (including bromsulphalein, thymol turbidity, cephalin-cholesterol flocculation test, alkaline phosphatase and serum van den Bergh), electrocardiogram, electroencephalogram and chest x-ray were normal. X-rays of the entire gastrointestinal tract and proctoscopic examination were negative. Lumbar puncture was performed and the spinal fluid dynamics, chemical tests and cell counts were normal. A search for microfilariae in the spinal fluid was negative. No trypanosomes were demonstrated by direct microscopic, cultural or animal inoculation technics. Multiple stool examination by direct, concentration and cultural technics were negative for ova and parasites. Serologic tests for syphilis were negative. Serologic tests for leishmania, trichina and endamoeba infections were negative. Notably, the complement-fixation test for filariasis, using Dirofilaria immitis antigen [*25*], was repeatedly negative. Microfilariae loa were readily demonstrated in both capillary and venous blood on fresh droplet examination and by stained preparations. They were definitely identified as being L. loa with hematoxylin and eosin preparations, and were described as sheathed worms of a length of approximately 275 microns, having body nuclei extending to the tip of the tail, and an external configuration that was most often angular and tortuous.

Periodicity study [*26*] of microfilariae in this patient was performed on capillary blood with 20 cu. mm. specimens in triplicate, counted and averaged every four hours over a five-day period. The result is illustrated in Figure 1.

During the first two weeks of hospitalization emotional upsets manifested by agitation were pronounced and were only partially controlled by barbiturates. These symptoms were worsened during a three-day premenstrual period.

Because of variable reactions occurring shortly after the initial use of hetrazan® [*4,5,13,27–40*], it was decided to begin therapy with very low doses of the drug. Accordingly, the patient was started on hetrazan on November 19, 1952, in doses of 0.25 mg. per kg. of body weight at six-hour intervals. Serial microfilarial counts were essentially unchanged during the following week and clinically the patient had no complaints or symptoms that were not present prior to initiation of therapy.

Because of this apparent lack of drug effect the dosage of hetrazan was increased after one week to 0.5 mg. per kg. of body weight at six-hour intervals. The response was dramatic. A marked decrease of microfilariae was noted. (Fig. 2.) Within twelve hours the patient became upset emotionally even more than usual. She complained of sharp right upper quadrant pain, unrelated to respiration, accompanied by anorexia, nausea and occasional vomiting. Additional complaints were mild chest pain, myalgia, arthralgia and pruritus (for the first time). The patient appeared to be quite ill.

Within twenty-four hours the liver became palpable 3 cm. below the right costal margin and was markedly tender. Because of the psychologic state of the patient biopsies of the liver were not obtained. Liver function tests now disclosed a 21 per cent bromsulphalein retention after forty-five minutes; thymol turbidity, cephalin-cholesterol flocculation test and serum bilirubin remained normal. Gamma globulin was increased to 12.5 units. Blood urea nitrogen was increased to 37 mg. per cent with normal urinalysis. The patient also noted a marked increase in the activity of the adult worms, and for the first time since her

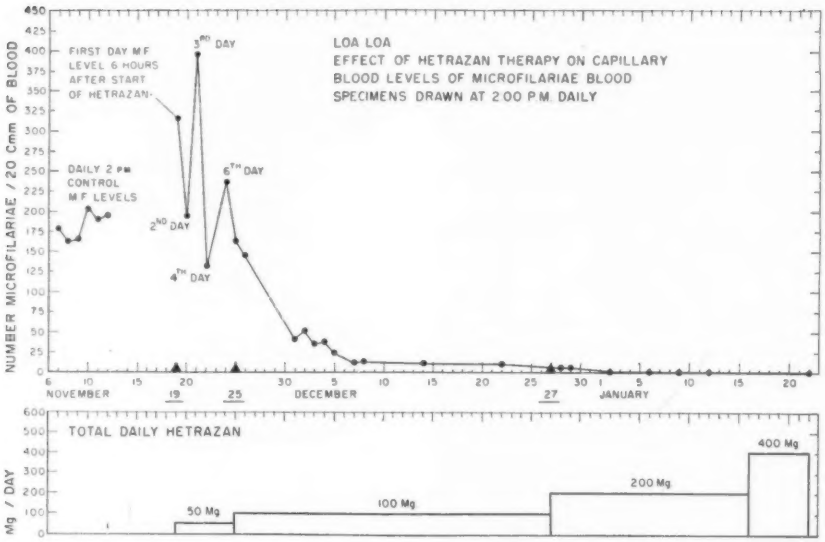

FIG. 2. Effect of hetrazan on daily peak microfilariae levels in this patient.

admission to the hospital they actually came to the surface of the skin. Hetrazan therapy was not stopped because it was anticipated that the hepatitis would subside in spite of continued therapy, as has been seen by others [*3–5,39*]. Four days later the liver had decreased in size and was less tender. Within a week it was no longer palpable and liver function tests reverted towards normal. The blood urea nitrogen had returned to normal. The total eosinophil count was now increased to 2,364 per cu. mm.

At the end of the second week of hetrazan therapy the initial episode of giant urticaria developed, the wheals being distributed primarily over the thighs, lower abdomen and back. The wheals were from 5 mm. to 2 cm. in diameter, hyperemic at the onset, fading after a few minutes with blanching at the periphery and occasional retention of a small spot of hyperemia in the center of the lesion. Rarely the wheals would start in the shape of a worm, with linear swellings preceding the urticarial spots by a few seconds or minutes. We were quite impressed by the patient's distressing complaints which initially were often subjective but frequently were followed within minutes or hours by the appearance of adult worms and urticariae in the exact skin areas which had been a site of complaint. Antihistaminics gave only moderate relief from the pruritus. (Fig. 3.)

After the third week of hetrazan therapy the patient had subjectively recovered from the hepatitis and was improved with regard to the adult worm activity. The remainder of the laboratory work may be seen in Figure 4 where the relation of the various laboratory findings to the antiparasitic drugs is shown. It is to be noted that most of the abnormal laboratory findings reached their peak during the third and fourth week of hetrazan therapy. For the first time the complement-fixation test for filariasis became strongly positive, then gradually declined during the next three weeks and again became negative. This occurred despite the continued presence of small numbers of circulating microfilariae. (Fig. 4.)

We now assumed that the total number of microfilariae had been so greatly reduced that an increase in hetrazan dosage would no longer have an adverse effect upon the liver. Thus the hetrazan dosage was further increased gradually (with microfilariae disappearing at 4 mg./kg. per day) until a level of 16 mg. per kg. of body weight per day was reached. The patient received a total of 17 gm. of hetrazan over a period of seventy-seven days. Six weeks after initiation of hetrazan therapy two small masses were felt in the deep subcutaneous tissues near the deltoid muscle insertion in both arms, and others were found later elsewhere. These initially appeared as tender, elongated masses approximately 3 cm. long which gradually lost their tenderness and decreased in size over a number of weeks. Permission for biopsy of the masses was not granted. At this same time an electrocardiogram disclosed an inversion of the T wave in lead AVF. This reverted to normal with continued hetrazan therapy one week later.

After five weeks of negative studies for circulating microfilariae and in spite of eleven weeks of hetrazan therapy the patient continued to be troubled occasionally, but quite severely, by the adult worm activity and accompanying urticarial reactions. Because hetrazan is only partially effective against adult filarial worms [*15,41*] it was decided to attempt eradication of the adult filariae by using a course of suramin (naphuride sodium) [*42–45*]. On February 6, 1953, a single intravenous injection of 0.25 gm. of suramin was given. Within ten minutes a solitary 2 cm. wheal developed over the left buttock, an area in which the patient had felt an irritation from a

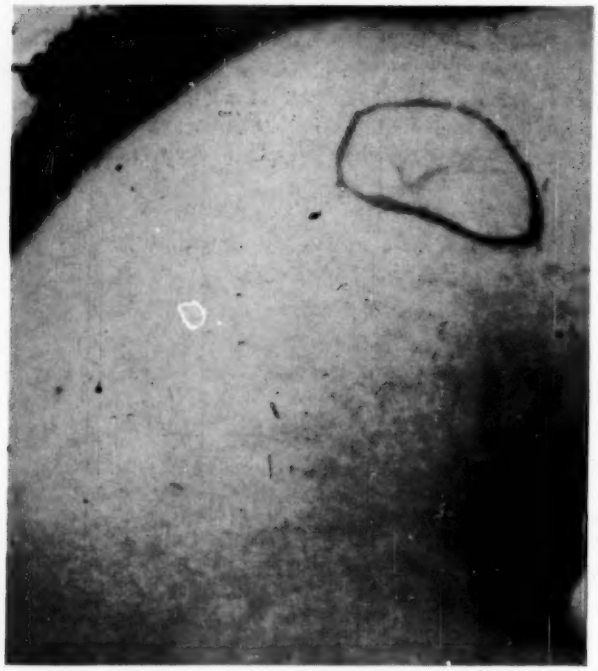

FIG. 3A. Filaria loa beneath skin on thigh in this patient.

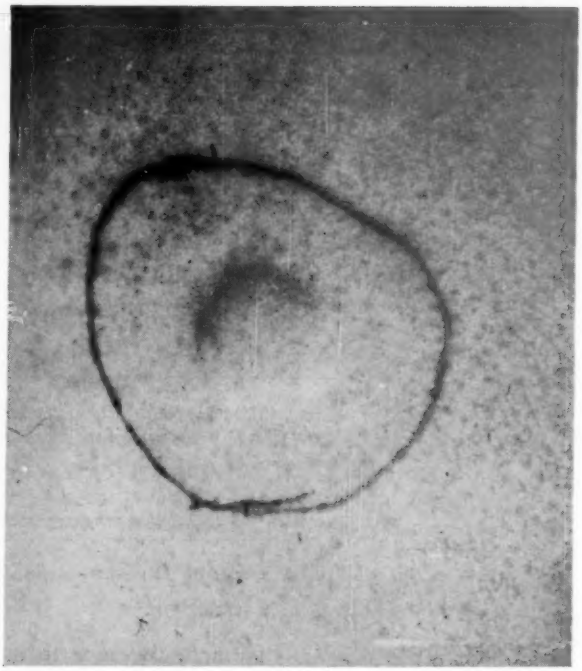

FIG. 3B. Urticarial wheal in same site as worm pictured in Figure 3A, which appeared thirty minutes after an intravenous injection of suramin.

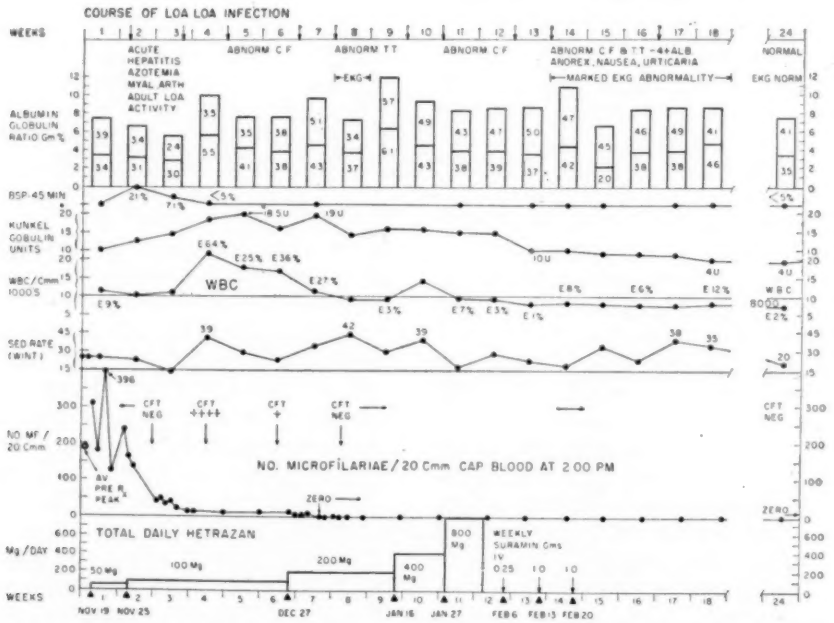

FIG. 4. Clinical laboratory studies in this patient with Loa loa as related to changes in therapy. C. F. = cephalin-cholesterol flocculation. T. T. = thymol turbidity. E. = per cent eosinophils on differential. C. F. T. = complement fixation test for filariasis.

crawling worm shortly before the injection. Five hours later she complained of generalized aching, malaise and nausea, but noted no additional adult worm activity. The following week was not remarkable. Laboratory findings remained unchanged.

On February 13 a second injection of 1.0 gm. of suramin was given intravenously. Thirty minutes later a solitary wheal appeared on the left buttock, starting in the shape of an adult worm and enlarging to a 1½ cm. diameter. It faded spontaneously after ten min-

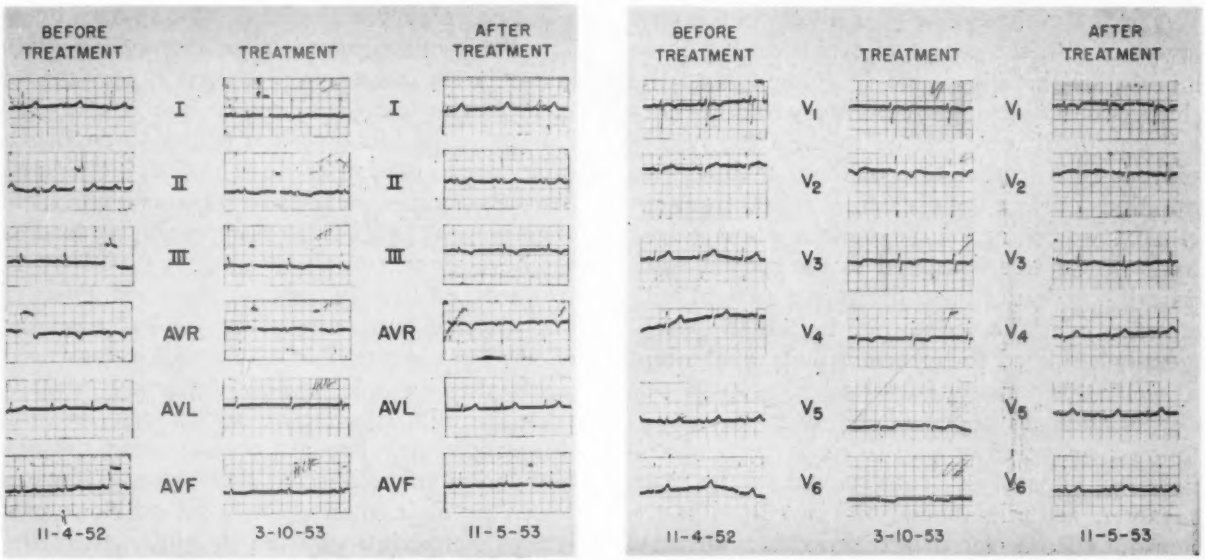

FIG. 5. Electrocardiographic changes illustrated in case of Loa loa during treatment with suramin.

utes. During the following week the only laboratory change was the development of a 1 to 2 + albuminuria.

On February 20 the patient received the third and last intravenous injection of 1.0 gm. of suramin without any immediate reaction developing. After approximately twelve hours she noticed a small Calabar swelling on the dorsal surface of the left wrist which subsided after an hour.

Three days later abdominal distention, crampy abdominal pain, nausea, anorexia, belching and complaints of flatus developed. This was followed by vomiting. There was marked increase in the complaints of worm activity but the worms were never seen after the second suramin injection. The cephalin-cholesterol flocculation test and the thymol turbidity again became transiently elevated. For the next two weeks she was quite ill, and symptoms became so severe that intravenous fluids had to be given daily. On March 2 additional hives on the back, arms, thighs and popliteal areas, a swollen and hot right elbow joint and severe edema of the right lower eyelid developed. Antihistaminics gave no relief. During this period electrocardiographic changes were again noted, but were more marked than with hetrazan, with inversion of all T waves (leads I, II, III, AVR, AVL, AVF, and V_1 to V_6). Serum electrolyte studies (potassium, sodium, calcium, phosphorus, chlorides and CO_2 combining power) were within normal limits. A therapeutic trial with oral potassium chloride failed to affect these changes. A Thorn test, performed with 100 mg. of cortisone, was normal. (Fig. 5.)

It was our interpretation that the observed abnormalities were not due to drug toxicity but to hypersensitivity to the filarial antigen. It was decided, therefore, during the fifteenth week of therapy to administer cortisone in order to affect the presumed antigen-antibody reaction. The initial dose of cortisone was 100 mg. per day. Dosage was gradually reduced during the following week and then discontinued. The clinical response was dramatic. Within twenty-four hours the patient was feeling better and took food for the first time in four days. Although she continued to have occasional urticariae while receiving cortisone, the accompanying subjective reactions became less severe and less frequent. The electrocardiogram was unaffected by cortisone but reverted to normal three weeks later. After discharge the patient was followed for an additional three years without medications. She no longer complains of malaise, lethargy, arthralgia or myalgia, and her mental attitude and alertness have improved greatly in contrast to her previous listless state. She feels better than at any time during the twelve years of infection and realizes, in retrospect, the severity and incapacitation of her chronic illness. All laboratory tests have remained normal.

COMMENTS

In this patient with chronic loiasis and marked parasitemia physical examination prior to treatment did not reveal any objective evidence of organic disorder. Except for the positive blood smears, the laboratory studies showed only slight and non-specific abnormalities. The scarcity of objective abnormal findings was in contrast to the patient's severe subjective complaints. It is of interest that during the early phase of the antiparasitic therapy objective evidence of severe multiple system involvement became manifest. This treatment eventually achieved elimination of circulating microfilariae, control of adult worm activity and marked subjective improvement.

A review of the twelve-year history of this case together with the course of events during three months of therapy make it evident that the changes of physical and laboratory findings during treatment were related to the therapy employed. In interpretation of these findings two questions present themselves. Was the transient clinical worsening of the patient due to drug toxicity? Or was it related to the specific antiparasitic action of these drugs in a patient with chronic loiasis, a condition in which pathogenesis is related to hypersensitivity of the host as well as to parasitic invasion?

The clinical abnormalities observed were as follows: severe emotional disturbance, abdominal symptomatology, enlargement of the liver, myalgia, arthralgia and joint swelling, angioneurotic edema, electrocardiographic evidence of carditis, increased surface activity of adult worms, recurrence of Calabar swellings and development of pruritus and giant urticaria for the first time in the patient's illness.

A survey of the abnormal laboratory findings revealed an increase in the leukocyte count, eosinophils, sedimentation rate, gamma globulin and blood urea nitrogen, also abnormal liver function tests and albuminuria. A markedly positive complement-fixation test for filariasis developed for the first time.

Some of the changes observed, such as the leukocytosis, elevated sedimentation rate and vague abdominal symptomatology were so nonspecific that their interpretation would be conjectural. They served mainly to emphasize the presence of organic disease in this patient in whom the original subjective complaints outweighed objective findings. Severe emotional disturbance and central nervous system involvement are known features in filariasis [*46,47*]. The clinical and laboratory findings consistent with an acute anicteric hepatitis during hetrazan therapy are noteworthy. Pharmacologic studies in dogs [*14*] gave no indication that hetrazan affects liver function, renal function, the hematopoetic system or the electrocardiogram. Clinical studies likewise have not suggested toxic effects on these organs. In the patient herein described, although elevation of blood urea nitrogen and acute hepatitis developed during the first week of therapy when small doses of the drug were administered, later on during the regimen an eightfold dose of hetrazan was tolerated without any observable undue reaction.

The mechanism of action of hetrazan in loiasis is not completely understood [*48–52*]. This drug is not microfilaricidal *in vitro*. It may affect the microfilariae as an opsonin, thereby facilitating their phagocytosis [*3,36*]. As the number of microfilariae in the blood stream begins to decrease, rapid accumulation of dead and dying microfilariae occurs in the liver with coincidental liver engorgement [*3,5*]. This may conceivably lead to the development of abnormal liver functions. It is of interest that, in the case presented, doses of 0.25 mg. of hetrazan per kg. of body weight effected no discernible change. An increased single dose of 0.5 mg./kg. apparently constituted a minimally effective or "critical" level for this patient, as it brought about a sharp drop in circulating microfilariae. This was rapidly followed by an exacerbation of all previous subjective complaints and the development of the acute objective illness described in the case report. Laboratory abnormalities reached their peak only two or three weeks after this exacerbation. This sequence of events, particularly with the notable development of a positive complement-fixation test with accompanying marked eosinophilia, indicates that, in addition to the mechanical effect of accumulation of microfilariae in the liver, antigen-antibody reactions also contributed to the pathogenesis of the observed illness. This interpretation is in accordance with the concept of other workers, namely that the clinical and laboratory changes during hetrazan therapy are due in large part to reactions of a hypersensitized host to newly liberated allergens [*53,55*]. In this case the strongly positive complement-fixation test, which slowly became negative with clinical improvement, is good evidence of the specificity of the allergic reaction, as this test is considered reliable when positive [*25*].

The critical or minimally effective dose of hetrazan for this patient did not suffice to eliminate the microfilariae. Capillary blood studies continued to be positive until the dosage of drug was increased about five weeks later to 1 mg./kg. every six hours. The need for large doses has been noted by others [*13,27*]. Once the microfilariae disappeared from the blood stream they never again became demonstrable by direct smear or by concentration technics during follow-up observation of three years. It can be assumed that some of the adult worms also were affected by hetrazan as their activity increased at the critical dosage level with prompt and active appearance in the cutaneous areas and

local allergic reaction. But activity of adult loa persisted despite the relatively large doses eventually employed, consistent with previous reports [*3,4,13,39*]. Unfortunately no methods are available to allow quantitative estimation of the effect of drugs on adult worms.

Suramin was administered in an attempt to achieve adult loa eradication. The most prominent events during suramin therapy were development of albuminuria, urticaria and marked electrocardiographic abnormality. Toxicity studies on suramin show primarily a chronic, cumulative renal irritation [*44,45*]. In view of the marked hypersensitivity aspect in loiasis and in this particular patient one may also postulate that the albuminuria is, at least in part, the result of host renal reaction to liberated antigen, or possibly to altered parasite protein. The angioneurotic edema and joint swelling observed during suramin therapy also may be interpreted as hypersensitivity reactions. The delayed host reaction to the drug correlates well with its slow action on adult loa [*56*]. In contrast, the cutaneous reactions of this patient occurred very soon after administration of the drug. This early allergic manifestation would suggest that the drug also has some immediate effect on the parasite.

The electrocardiographic abnormalities noted during hetrazan and more prominently during and after suramin therapy were of particular interest. These changes during hetrazan therapy were slight and resolved while hetrazan was still being administered. In view of this it would be difficult to attribute them to drug toxicity. There are also no reports in the literature that electrocardiographic changes are caused by suramin which has been used extensively in African trypanosomiasis. Therefore it seems quite unlikely that the cardiac involvement noted in this case was related to drug toxicity. Electrolyte shift was considered as a possible cause of the electrocardiographic changes noted in this patient, but was not demonstrable.

Localization of adult loa in the heart has been reported [*6*]. Electrocardiographic changes might therefore result from the presence of adult worms in the myocardium. Such changes were not present before therapy. They occurred in this patient simultaneously with increased adult worm activity with associated visible allergic phenomena. They were more pronounced and protracted during suramin therapy. This is felt to be significant as suramin has more effect on adult loa than hetrazan. It is conceivable that increased activity of adult worms and dead and disintegrating loa localized in the myocardium could incite a local allergic reaction and that the associated inflammation could persist for several weeks [*57*]. It is postulated that in this case of loiasis the electrocardiographic changes were a reflection of an allergic carditis, brought about by destruction of the parasite by the drugs employed. It has been reported by Mikulichick [*58*] that in rabbits exposed to antigen-antibody reactions almost 100 per cent of the hearts examined showed anaphylactic "cell injury." The occurrence of an allergic carditis has been considered in another parasitic disease, trichinosis, where local parasitization of the heart as well as abnormal electrocardiograms without apparent parasitization have been noted [*59–61*]. To our knowledge allergic carditis as an expression of an antigen-antibody reaction in loiasis has not been previously reported. In this patient the intensity of the cardiac reaction was not severe enough to cause clinical signs of cardiac embarrassment. Follow-up studies have shown that electrocardiographic changes were reversible in this case.

It has been stated in the case report that this patient was initially treated with relatively small doses of hetrazan and that increase in dosage was accomplished only gradually. Such gradual and cautious medication appears advisable in infectious diseases in which the host may have become markedly hypersensitive to the infectious agent or its products. Frequently a certain equilibrium appears to develop between host and parasite. Disturbance of this balance may occur during specific therapy directed against the inciting antigen. Initial large doses of the specific therapeutic agent may then call forth a marked antigen-antibody reaction which manifests itself as severe clinical illness. In spite of the initial small doses employed, this patient experienced a moderately severe exacerbation of her illness during therapy. With clinical improvement larger doses of hetrazan were eventually well tolerated. It is impossible to state whether or not this patient would have tolerated larger doses on protracted therapy with suramin. However the risk of possibly prolonging or worsening the course of the allergic, therapeutically induced carditis did not appear justified.

This patient has shown no evidence of a return of subjective symptoms or of objective evidence of parasite activity during the three years since

termination of therapy. We feel justified in regarding her as being in a state of therapeutic remission which, it is to be hoped, will prove to be permanent.

SUMMARY

1. A case report is presented of a patient heavily infected with L. loa. The infection was known to have exceeded twelve years in duration.

2. The patient was treated with hetrazan and suramin. A therapeutic remission was obtained.

3. The host reactions to destruction of microfilariae by hetrazan and to destruction of adult loa by suramin are described. These consisted of the development of a positive complement-fixation test for filariasis and frank allergic cutaneous manifestations. In addition there were gastrointestinal and central nervous system manifestations. Acute anicteric hepatitis and myocarditis also occurred.

4. The possible mechanism of these reactions is discussed in terms of an altered host-parasite relationship.

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SUBJECT INDEX VOLUME XXII

(ab.) = Abstracts; (CPC) = Clinico-pathologic Conference; (E.) = Editorial

Subject Index

Subject Index

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SUBJECT INDEX VOLUME XXII

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Subject Index

The American Journal of Medicine

The American Journal of Medicine

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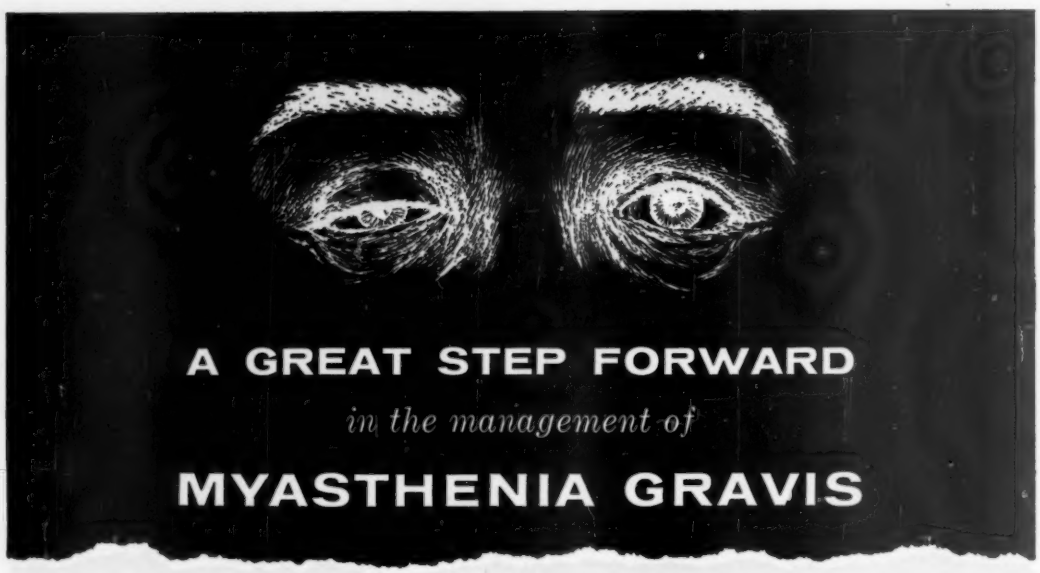

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1. Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: *J.A.M.A.*, 158:625, June 25, 1955.
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The American Journal of Medicine

Vol. XXII JUNE, 1957 No. 6

Editorial

Clinical Studies

The thesis set forth in this paper is that pleuropneumonia-like organisms can be obtained in pure culture from the urine of some patients with acute abacterial pyuria (acute hemorrhagic cystitis) under circumstances which suggest an etiologic relationship. Despite the controversial status of these organisms in the pathogenesis of disease, a strong case for them is made. Of interest is the account of involvement of the urethra, eyes, joints and skin in association with acute hemorrhagic cystitis in some cases in which pleuropneumonia-like organisms were found. The relationship to Reiter's syndrome, which is briefly discussed, requires further clarification.

This is an enlightening review of the experience with Klebsiella meningitis as described in the literature and encountered by the authors. Problems of classification and management are discussed, with special reference to the use of sulfonamides and broad-spectrum antibiotics.

This paper describes thirteen cases presenting the all too familiar problem of fungus infection complicating antibiotic and/or steroid therapy, particularly in debilitated patients. A distinction is made between surface and invasive fungal lesions.

Aspiration pleural biopsy was performed in forty-five patients with pleural effusion, and proved to be a simple, safe, rapid and relatively effective procedure for establishing the etiology in most

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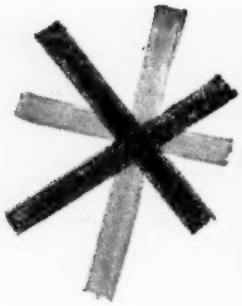

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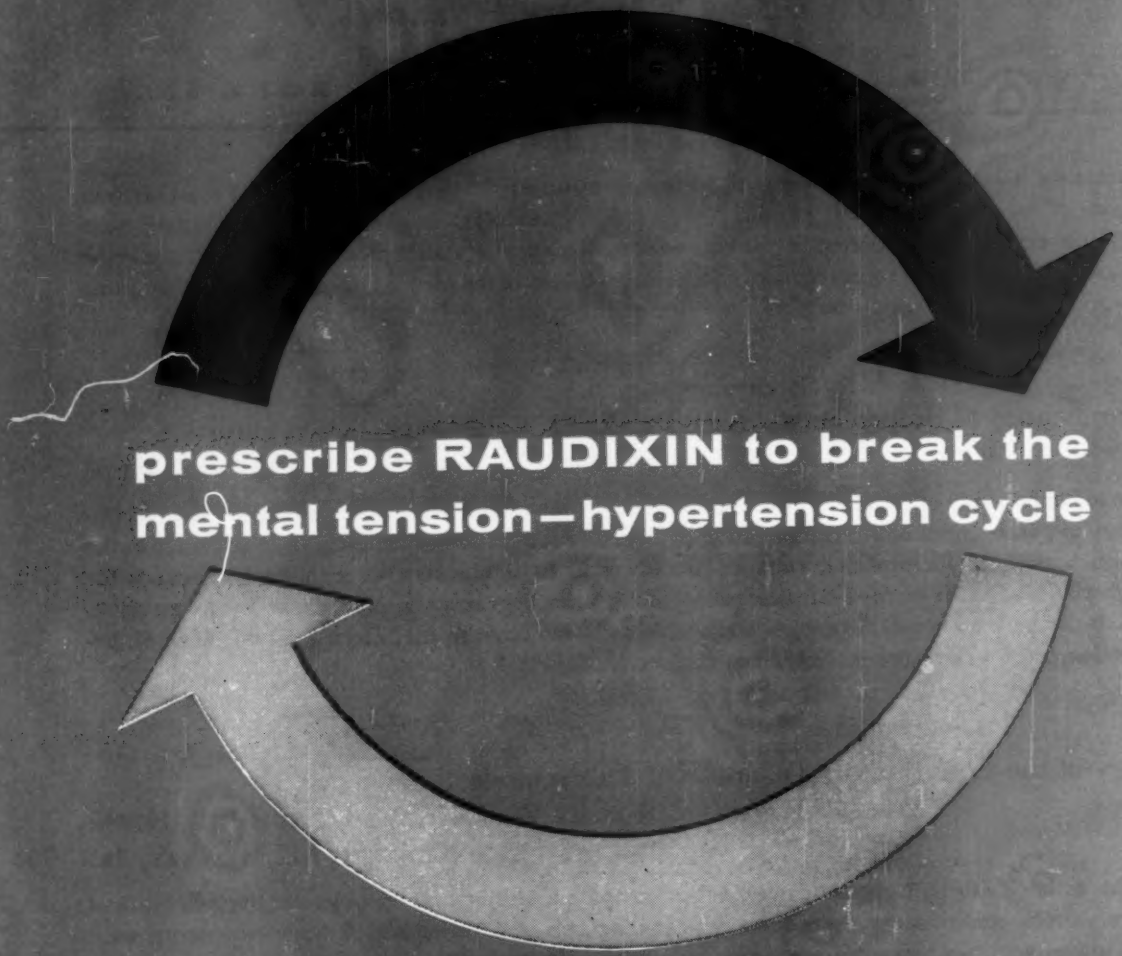

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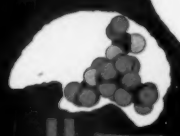

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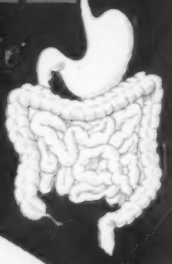

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(must be adjusted to patient's response)

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If previous insulin dosage was
less than
40 u./day . . . reduce insulin 30% to 50% immediately; gradually reduce insulin dose if response to Orinase is observed.

more than
40 u./day . . . reduce insulin 20% immediately; carefully reduce insulin beyond this point if response to Orinase is observed. In these patients, hospitalization should be considered during the transition period.

Caution: During the initial "test" period (not more than 5 to 7 days), the patient should test his urine for sugar and ketone bodies three times daily and report to his physician daily. For the first month, he should report at least once weekly for physical examination, blood sugar determination, and white cell count (with differential count, if indicated). After the first month, the patient should be seen at least once a month, and the above studies carried out.

It is especially important that the patient, because of the simplicity and ease of administration of Orinase, does not develop a careless attitude ("cheating" on his diet, for example) which may result in serious consequences and failure of treatment.

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Indications. Orinase is most likely to benefit the patient in whom the diabetes is relatively mild and stable, is not adequately controlled by dietary restrictions alone, and developed sometime after the age of 30 years.

Contraindications. Orinase is contraindicated in patients with 1) diabetes of the types known variously as juvenile, growth-onset, unstable, or brittle; 2) a history of diabetic coma; 3) diabetes complicated by ketosis, acidosis, coma, fever, severe trauma, gangrene, Raynaud's disease, or serious impairment of renal or thyroid function; 4) hepatic dysfunction; and 5) diabetes adequately controlled by dietary restriction.

Effects. In patients with a satisfactory response to Orinase, the blood sugar falls, glycosuria diminishes, and such symptoms as pruritus, polyuria, and polyphagia disappear. It is *not* a substitute for insulin. And it requires the same adherence to basic principles of diabetes control as does insulin, e.g., dietary regulation; tests for glycosuria and ketonuria; hygiene; exercise; instruction of the patient to recognize and counteract impending hypoglycemia, to follow rigidly directions regarding diet and continuing use of the drug and to report immediately to the physician any feeling of illness. Extreme care must be taken during the transition period to avoid ketosis, acidosis, and coma.

Side effects. To date, the most serious side effect is hypoglycemia, which may occur occasionally and is most likely to occur during the transition period from insulin to Orinase. Other untoward reactions to Orinase are rare, usually of a nonserious nature, and tend to disappear on adjustment of dosage, e.g., gastrointestinal disturbances, headache, variable allergic skin manifestations, and alcohol intolerance.

Clinical toxicity. Aside from an occasional hypoglycemia, Orinase appears to be remarkably free of gross clinical toxicity. There is no evidence of crystalluria or other untoward effects on renal function, or of hepatotoxicity. Except for a rare leukopenia of mild degree, which has been reversible (in some instances, even under continued therapy), there have been no adverse effects on hematopoietic function.

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Q. What is Marsilid?

A. Marsilid (iproniazid) is an amine oxidase inhibitor which affects the metabolism of serotonin, epinephrine, norepinephrine and other amines.

Q. How does Marsilid act?

A. Marsilid has a normal eudaemonic* rather than an abnormal euphoric effect; it promotes a feeling of well-being and increased vitality; it restores depleted energy and stimulates appetite and weight gain in chronic debilitating disorders.

Q. How soon is the effect of Marsilid apparent?

A. Marsilid is a slow-acting drug. In mild depression it usually takes effect within a week or two; in severe psychotics, results may be apparent only after a month or more.

Q. What are the indications for Marsilid?

A. Mild depression in ambulatory, non-psychotic patients; psychoses associated with severe depression or regression; stimulation of appetite and weight gain in debilitated patients; chronic debilitating disorders; stimulation of wound healing in draining sinuses (both tuberculous and non-tuberculous); adjunctive therapy in rheumatoid arthritis when associated with depressed

*Eudaemonia is a feeling of well-being or happiness; in Aristotle's use, felicity resulting from life of activity in accordance with reason.

a psychic energizer

(the opposite of a tranquilizer)

psychomotor activity (Marsilid stimulates physical and mental activity, appetite and weight gain without objective joint changes).

Q. What is the dosage of Marsilid?

A. The daily dose of Marsilid should not exceed 150 mg (50 mg t.i.d.). In patients who are not hospitalized, the dosage should be reduced after the first 8 weeks to an average of 50 mg daily or less, for Marsilid is a cumulative drug. Like all potent drugs, Marsilid requires careful individual dosage adjustment.

Q. What are the potential side effects of Marsilid?

A. Side effects due to Marsilid are reversible upon reduction of dosage or cessation of therapy. It may cause constipation, hyperreflexia, paresthesias, dizziness, postural hypotension, sweating, dryness of mouth, delay in starting micturition, and impotence.

Q. When is Marsilid contraindicated?

A. Marsilid is contraindicated in overactive, overstimulated or agitated patients. Marsilid therapy should be discontinued two days before the use of ether anesthesia. It should not be given together with cocaine or meperidine. In patients with impaired kidney function, Marsilid should be used cautiously to prevent accumulation. Marsilid is not recommended in epileptic patients.

Q. How is Marsilid supplied?

A. Marsilid is supplied in scored 50-mg, 25-mg and 10-mg tablets.

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4. Vitamin C increases the availability of iron for hemoglobin and red blood cell formation, as well as to build body reserves.
5. The combination of iron and vitamin C is likely to be better tolerated than iron alone.

"Cytoferin" Tablets—No. 705, bottles of 100 and 1,000. "Cytoferin" Liquid—No. 945, bottles of 8 fluidounces. Stable liquid preparation; nonalcoholic; extremely palatable; may be taken undiluted.

Each tablet or 10 cc. (2 tsp.) contains:

Ferrous sulfate* (3 gr.)	200 mg.
Vitamin C (ascorbic acid)	150 mg.

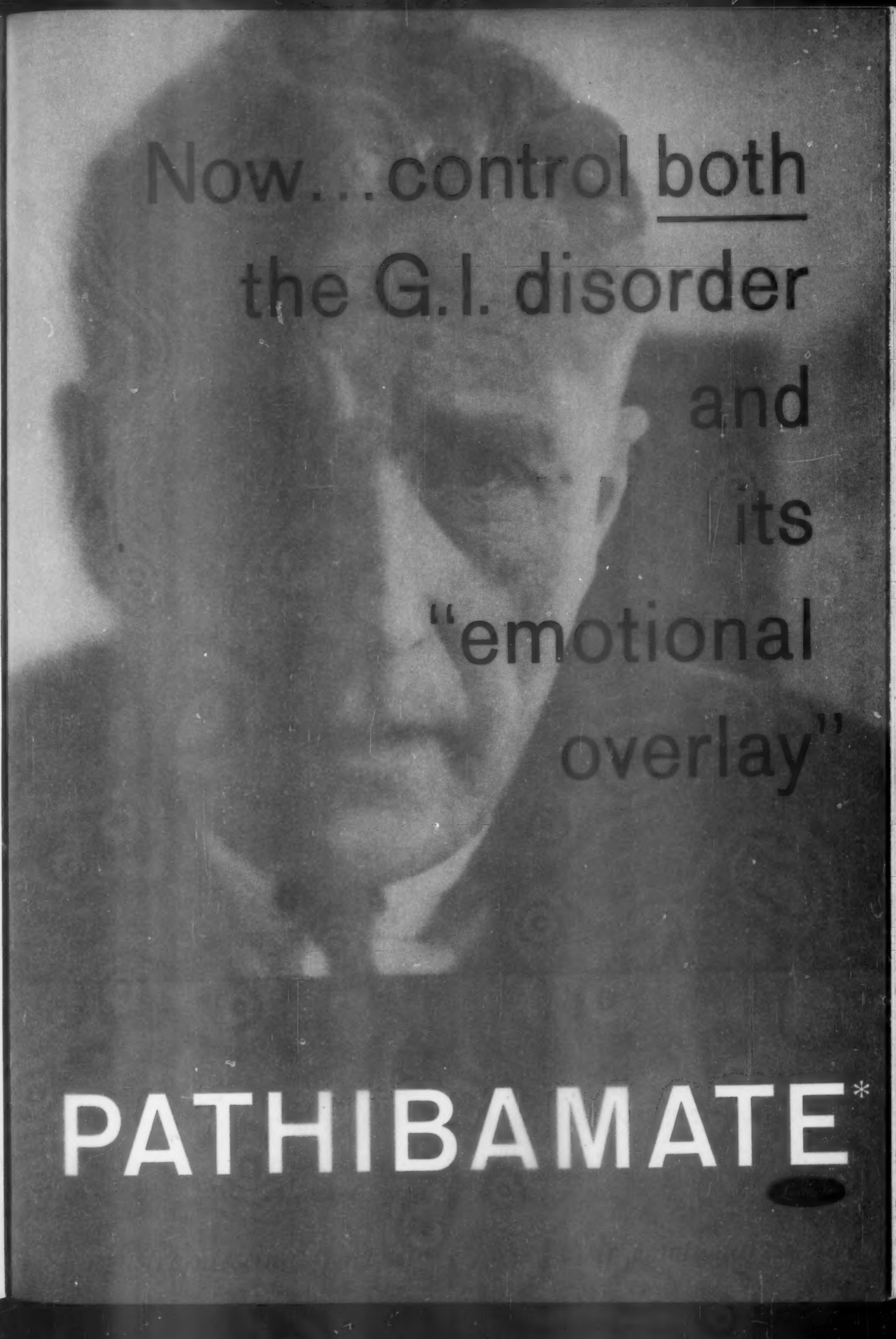
*Exsiccated in the tablets, and U.S.P. in the liquid.

Suggested dosages: To be taken preferably with meals. Adults and children: 1 tablet or 2 teaspoonfuls (10 cc.) two or three times daily. Infants and children: 1 teaspoonful (5 cc.) two or three times daily depending on age.

Bibliography available on request.

Ayerst AYERST LABORATORIES • NEW YORK, N.Y. • MONTREAL, CANADA

5713


Now...control both
the G.I. disorder
and
its
"emotional
overlay"
PATHIBAMATE*

PATHIB

combines **Meprobamate** *(400 mg.):*

Widely prescribed tranquilizer-muscle relaxant. Effectiveness in anxiety and tension states clinically demonstrated in millions of patients. Meprobamate acts only on the central nervous system. Does not increase gastric acid secretion. It has no known contraindications, can be used over long periods of time.[1,2,3]

with **Pathilon** *(25 mg.):*

An anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of G.I. tract disorders. In a comparative evaluation of currently employed anticholinergic drugs, PATHILON ranked high in clinical results, with few side effects, minimal complications, and few recurrences.[4]

Now...with **PATHIBAMATE**...*you can control disorders of the digestive tract and the "emotional overlay" so often associated with their origin and perpetuation...without fear of barbiturate loginess, hangover or addiction. Among the conditions which have shown dramatic response to* **PATHIBAMATE** *therapy:*

DUODENAL ULCER • GASTRIC ULCER • INTESTINAL COLIC
SPASTIC AND IRRITABLE COLON • ILEITIS • ESOPHAGEAL SPASM
ANXIETY NEUROSIS WITH G.I. SYMPTOMS • GASTRIC HYPERMOTILITY

BAMATE

Comments on PATHIBAMATE *from clinical investigators*

• "I find it easy to keep patients using the drug continuously and faithfully. I feel sure this is due to the desirable effect of the tranquilizing drug."[5]

• "The results in several people who were previously on belladonna-phenobarbital preparations are particularly interesting. Several people volunteered that they felt a great deal better on the present medication and noted less of the loginess associated with barbiturate administration."[6]

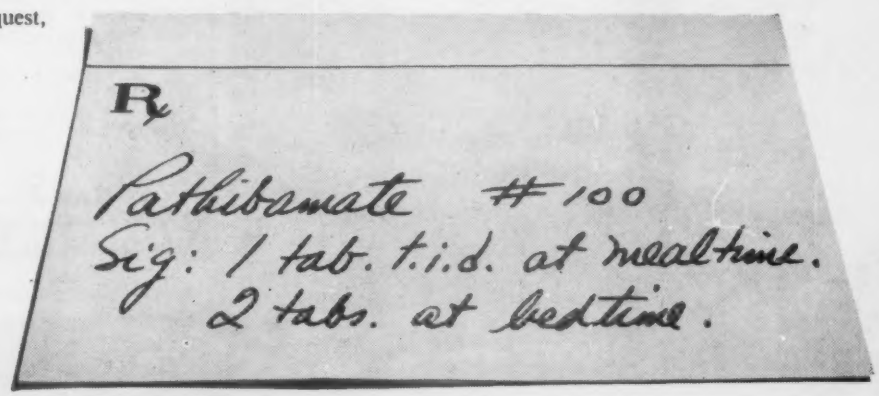
• PATHIBAMATE..."will favorably influence a majority of subjects suffering from various forms of gastrointestinal neurosis in which spasmodic manifestations and nervous tension are major clinical symptoms."[7]

• "In the patients with functional disturbances of the colon with a high emotional overlay, this has been to date a most effective drug."[5]

References: 1. Borrus, J. C.: *M. Clin. North America,* In press, 1957. 2. Gillette, H. E.: *Internat. Rec. Med. & G. P. Clin.* 169:453, 1956. 3. Pennington, V. M.: *J.A.M.A.,* In press, 1957. 4. Cayer, D.: Prolonged Anticholinergic Therapy of Duodenal Ulcer. Am. J. Dig. Dis. 1:301-309 (July) 1956. 5. McGlone, F. B.: Personal Communication to Lederle Laboratories. 6. Texter, E. C., Jr.: Personal Communication to Lederle Laboratories. 7. Bauer, H. G. and McGavack, T. H.: Personal Communication to Lederle Laboratories.

Supplied: Bottles of 100 and 1000

Administration and Dosage: 1 tablet three times a day at mealtimes and 2 tablets at bedtime. Full information on PATHIBAMATE available on request, or see your local Lederle representative.



now...

to complete the Parke-Davis f

CELONTIN Kapseals (Methsuximide, Parke-Davis)
0.3 Gm., bottles of 100.
DILANTIN® Sodium (Diphenylhydantoin Sodium, Parke-Davis)
is supplied in a variety of forms—including
Kapseals of 0.03 Gm. and 0.1 Gm. in bottles of 100 and 1,000.
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30 mg., desoxyephedrine hydrochloride 2.5 mg.), bottles of 100.

family of anticonvulsants

a new antiepileptic for petit mal and psychomotor seizures

CELONTIN*

(methsuximide, Parke-Davis)

Kapseals®

Clinical experience[1,2,3] with CELONTIN indicates that it:

- provides effective control with minimal side effects in the treatment of petit mal and psychomotor epilepsy;
- frequently checks seizures in patients refractory to other medications;
- has not been observed to increase incidence or severity of grand mal attacks in patients with combined petit and grand mal seizures.

Optimal dosage of CELONTIN should be determined by individual needs of each patient. A suggested dosage schedule is one 0.3 Gm. Kapseal daily for the first week. If required, dosage may be increased thereafter at weekly intervals, by one Kapseal per day for three weeks, to maximum total daily dosage of four Kapseals (1.2 Gm.).

1. Zimmerman, F. T., and Burgemeister, B.: *Arch. Neurol. & Psychiat.* 72:720, 1954.
2. Zimmerman, F. T., and Burgemeister, B.: *J.A.M.A.* 157:1194, 1955.
3. Zimmerman, F. T.: *Arch. Neurol. & Psychiat.* 76:65, 1956.

*TRADEMARK

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NOW—the unequalled advantages of K_1—orally

Tablets

MEPHYTON®

(VITAMIN K_1, MERCK)

"... vitamin K_1 is more effective than any other agent now available in combating drug-induced hypoprothrombinemia."[1] "Vitamin K_1 appears to be equally effective by the oral or intravenous route."[2] Beneficial effects are apparent in 6 to 10 hours following oral use.

Supplied: Oral MEPHYTON—tablets of 5 mg. of vitamin K_1, in bottles of 100. Emulsion of MEPHYTON—in boxes of six 1-cc. ampuls, 50 mg. of K_1 per cc.

References: 1. Gamble, J.R., et al. Arch. Int. Med. 95:52, 1955. 2. Gamble, J.R., et al. J. Lab. & Clin. Med. 42:805, 1953.

MSD

MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC. PHILADELPHIA 1, PA.

a NEW spasmolytic drug

for skeletal muscle spasm

Disipal®*

Brand of Orphenadrine HCl

- orally effective
- relatively long-acting
- minimal side actions
- nonsoporific
- tolerance no problem
- no known organic contraindications

Effective

for the Symptomatic Relief of Muscle Spasm in

Parkinsonism of all types	Whiplash injuries
Low back pain	Torticollis
Herniated intervertebral disc	Hemiballism
Fibrositis	Huntington's chorea
	Cerebral palsy

*Trademark of Brocades-Stheeman & Pharmacia
U.S. Patent No. 2,567,351. Other patents pending.

In addition to its spasmolytic effect, Disipal evokes a mildly euphoric response, particularly valuable in the Parkinsonian patient.

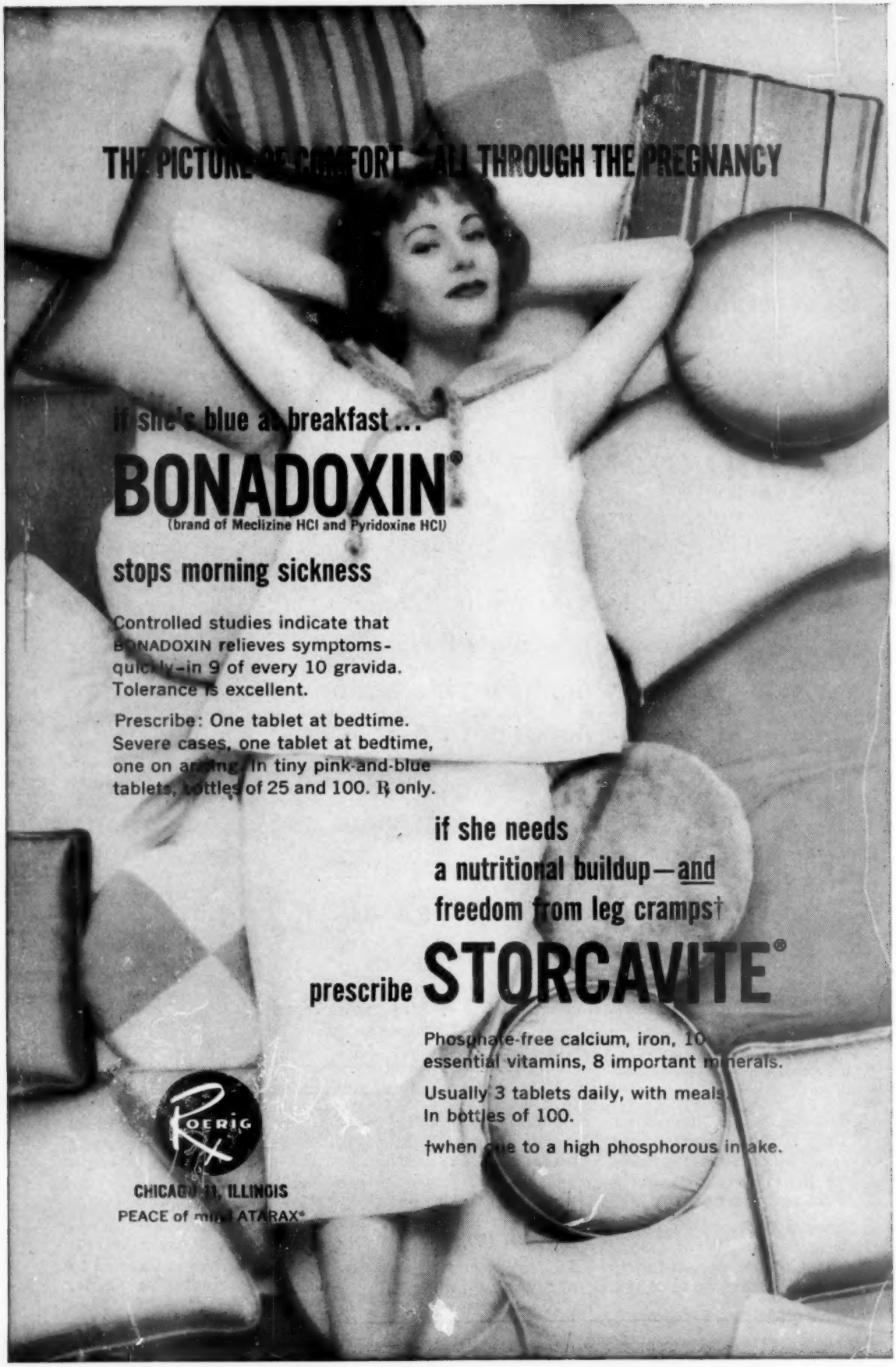
Disipal is nonsoporific. Continuous therapy for as long as 44 months produced no serious ill effect, no tolerance.

In 480 cases of Parkinsonism (arteriosclerotic, postencephalitic, and idiopathic), 50 investigators reported good to excellent results in 286 (59%), and fair in 97 (20.2%).

In 120 cases of other types of muscle spasm, good results were obtained in 59 (49.1%) and fair results in 24 (20.1%). Side effects are minimal.

Dosage: Initially 1 tablet (50 mg.) t.i.d. In combination with other spasmolytic drugs, dosage is titrated to meet individual needs.

Riker
Los Angeles


THE PICTURE OF COMFORT—ALL THROUGH THE PREGNANCY
if she's blue at breakfast...
BONADOXIN®
(brand of Meclizine HCl and Pyridoxine HCl)
stops morning sickness
Controlled studies indicate that BONADOXIN relieves symptoms-quickly-in 9 of every 10 gravida. Tolerance is excellent.
Prescribe: One tablet at bedtime. Severe cases, one tablet at bedtime, one on arising. In tiny pink-and-blue tablets, bottles of 25 and 100. ℞ only.
if she needs
a nutritional buildup—and
freedom from leg cramps†
prescribe STORCAVITE®
Phosphate-free calcium, iron, 10 essential vitamins, 8 important minerals.
Usually 3 tablets daily, with meals. In bottles of 100.
†when due to a high phosphorous intake.
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PEACE of mind ATARAX®

***Times Square's** largest sign isn't big enough to cover all the pages of scientific reports published on GANTRISIN.

The efficacy of GANTRISIN as an antibacterial agent is recognized everywhere. Of its ten forms it can be said that each provides an action against infections that is decisive, rapid, enduring and, above all, well tolerated.

Lipo gantrisin
for infections
in children -

LIPO GANTRISIN

'ROCHE'

provides therapeutic blood levels of time-proved Gantrisin around-the-clock—with only two doses daily.

DESCRIPTION:

Lipo Gantrisin should be considered for use in many systemic and urinary tract infections because it provides:

1. the time-proved wide-spectrum antibacterial action of Gantrisin in a stable, free-flowing homogenized emulsion
2. convenience of therapeutic blood levels for 24 hours with just two daily doses
3. delicious taste that assures wide acceptance by children and adults
4. no need for forced fluids . . . no danger of renal blocking or secondary fungus growth

INDICATIONS:

Systemic and urinary tract infections due to streptococci, staphylococci, pneumococci, H. influenzae, K. pneumoniae, meningococci, E. coli, B. proteus, B. pyocyaneus, A. aerogenes, B. paracolon and Alcaligenes fecalis.

DOSAGE:

Children:	teaspoonfuls every 12 hours
20 lbs	1
40 lbs	1½
60 lbs	2
80 lbs	3
Adults:	4

CAUTION:

The usual precautions in sulfonamide therapy should be observed.

SUPPLIED:

Lipo Gantrisin Acetyl, containing 20 per cent Gantrisin (1 Gm per 5 cc in the form of Gantrisin Acetyl), in a palatable, readily digestible homogenized emulsion that prolongs the action of the drug. In bottles of 4 and 16 oz.

Lipo Gantrisin® Acetyl – brand of acetyl sulfisoxazole in vegetable oil emulsion

ROCHE

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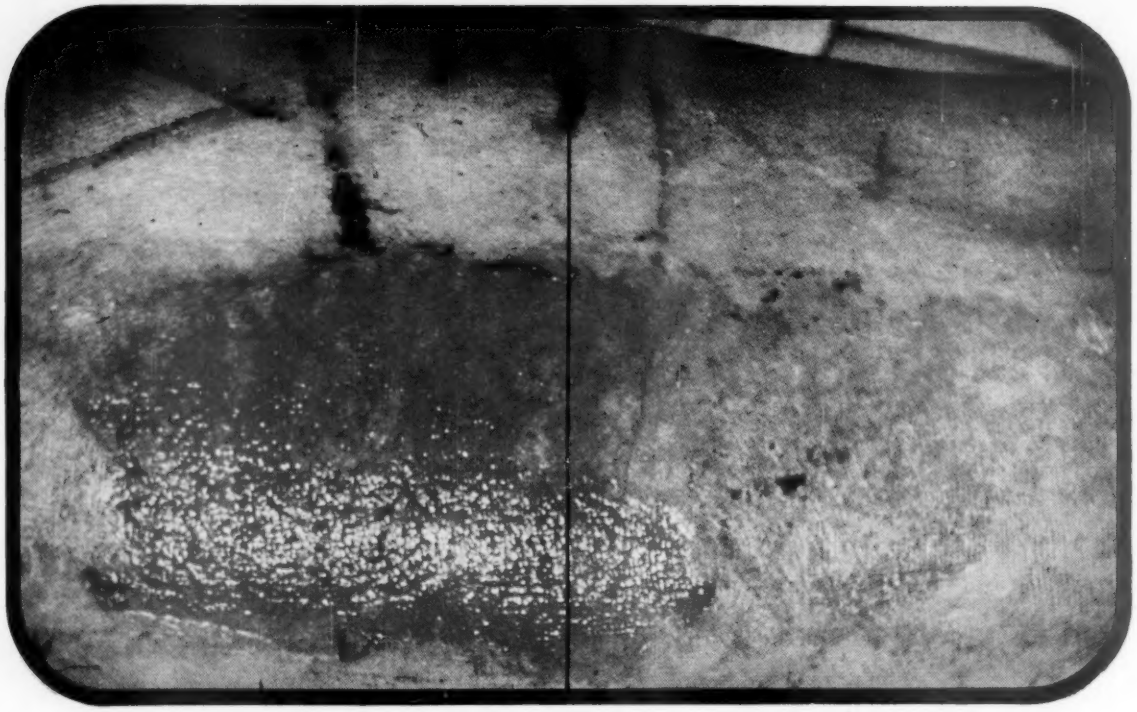


Skin graft donor site after 2 weeks' treatment with...

petrolatum gauze—still largely granulation tissue | FURACIN gauze—completely epithelialized

OBJECTIVE EVIDENCE OF SUPERIOR WOUND HEALING

was obtained in a quantitative study of 50 donor sites, each dressed half with FURACIN gauze, half with petrolatum gauze. Use of antibacterial FURACIN Soluble Dressing, with its water-soluble base, resulted in more rapid and complete epithelialization. No tissue maceration occurred in FURACIN-treated areas. There was no sensitization.

Jeffords, J. V., and Hagerty, R. F.: Ann. Surg. *145*:169, 1957.

FURACIN®. . . brand of nitrofurazone
the broad-range bactericide that is *gentle to tissues*

spread FURACIN Soluble Dressing: FURACIN 0.2% in water-soluble ointment-like base of polyethylene glycols.

sprinkle FURACIN Soluble Powder: FURACIN 0.2% in powder base of water-soluble polyethylene glycols. Shaker-top vial.

spray FURACIN Solution: FURACIN 0.2% in liquid vehicle of polyethylene glycols 65%, wetting agent 0.3% and water.

EATON LABORATORIES, NORWICH, N.Y.

Nitrofurans—a NEW *class of antimicrobials—neither antibiotics nor sulfonamides*

Corn oil lowers **serum cholesterol**

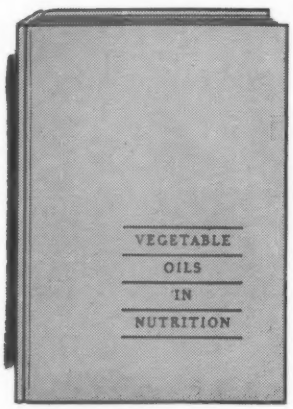
Physicians are well aware of recent reports that blood cholesterol levels tend to decrease significantly in humans when a substantial part of the dietary fat is supplied as polyunsaturated vegetable oil. Many clinical and experimental studies have shown Mazola Corn Oil to be particularly effective as a cholesterol-reducing agent.

In the dietary management of blood cholesterol levels it is practical to decrease the total daily intake of fat and substitute Mazola Corn Oil for a substantial amount of the saturated fat. Corn oil can be included in the daily diet as salad dressings and in a variety of other ways* without the usual inconveniences of dieting. Mazola Corn Oil is a product everyone knows, respects, enjoys and keeps on hand.

MAZOLA® CORN OIL IS DERIVED 100% FROM CORN

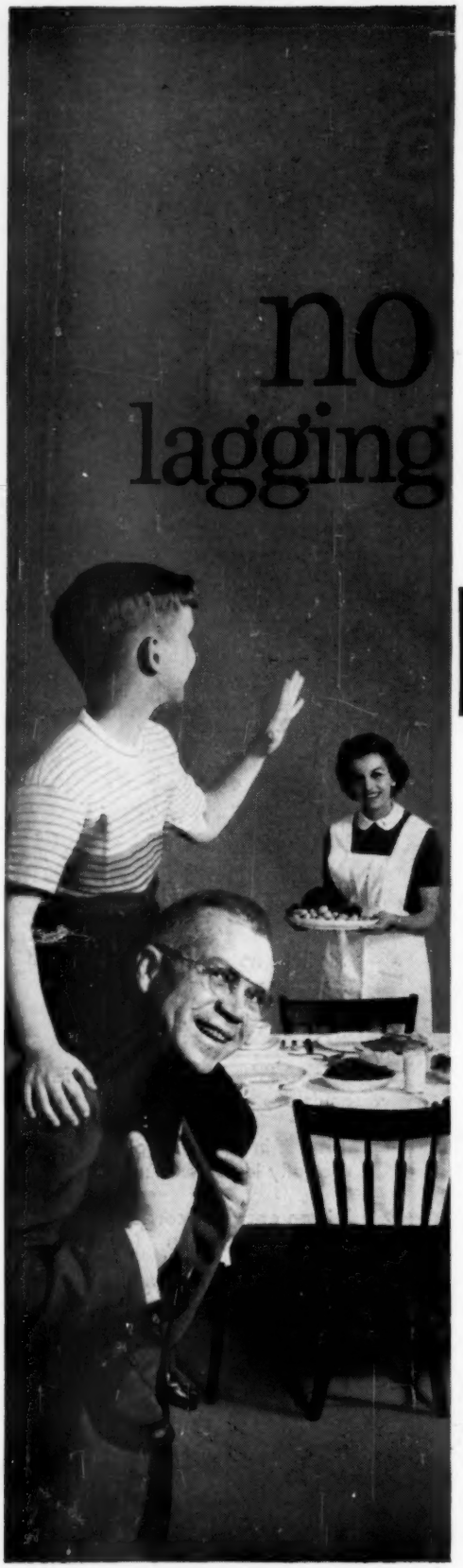
- It is in its natural form—*not hydrogenated*
- It contains no cholesterol
- Over 85% of its component fatty acids are unsaturated
- It is rich in the metabolically specially important linoleic acid
- It is an excellent carrier for fat soluble vitamins
- It is well tolerated, readily digested and easily absorbed
- It is suitable for inclusion in the daily diet in a wide variety of ways*

**A collection of recipes using Mazola Corn Oil is available on request.*



Do you have "Vegetable Oils in Nutrition?" If not, you may have this 88-page reference and monograph without charge. Write to Medical Department, Corn Products Refining Company, 17 Battery Place, New York 4, N. Y.

CORN PRODUCTS REFINING COMPANY



appetites with INCREMIN*

LYSINE-VITAMIN SUPPLEMENT LEDERLE

Finicky eaters are headed for a fast nutritional build-up with INCREMIN—tasty appetite stimulant.

INCREMIN offers l-Lysine for improved protein utilization, and essential vitamins for their stimulating effect on appetite.

Tasty INCREMIN is available in either Drops or Tablets. Caramel-flavored Tablets may be orally dissolved, chewed or swallowed. Cherry-flavored Drops may be mixed with milk, formula or other liquid. Tablets: bottles of 30. Drops: plastic dropper-type bottle of 15 cc.

Each INCREMIN Tablet
or each cc. of INCREMIN Drops *contains:*

l-Lysine	300 mg.	Pyridoxine (B_6)	5 mg.
Vitamin B_{12}	25 mcgm.	(INCREMIN Drops contain 1%	
Thiamine (B_1)	10 mg.	alcohol)	

Dosage: only 1 INCREMIN Tablet or 10-20 INCREMIN Drops daily.

*REG. U. S. PAT. OFF.

LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK

Lederle

Your restless patients' sleep problems
can be managed conservatively
prescribe **NOCTEC**

Squibb Chloral Hydrate

"The general practitioner likes it..."
"...can be given to patients of all ages and physical status..."

"...patients with cardiac disease..."
"...no proof that it is deleterious to the heart..."

"The psychiatrist often finds it the agent of choice..."
"...much less likely to produce mental excitement..."

"...frequently the favorite of the dermatologist..."
"...skin reactions from it are uncommon..."

Current Concepts in Therapy: Sedative-Hypnotic Drugs.
II. Chloral Hydrate. New England J. Med. 255:706 (Oct. 11) 1956.
adults: 1 or 2 7½ gr. capsules or 1 or 2 teaspoonfuls of Noctec Solution 15 to 30 minutes before bedtime.
children: 1 or 2 3¾ gr. capsules or ¼ to 1 teaspoonful of Noctec Solution 15 to 30 minutes before bedtime.
7½ and 3¾ gr. capsules, bottles of 100.
Solution, 7½ gr. per 5 cc. tsp., bottles of 1 pint.

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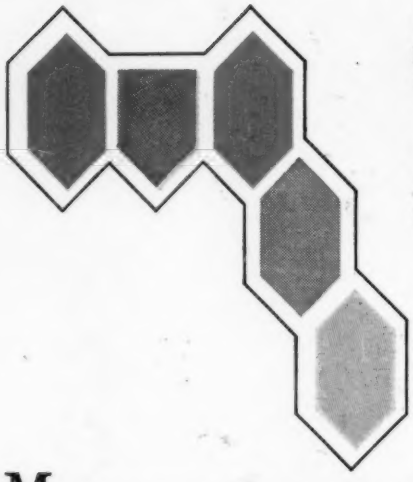
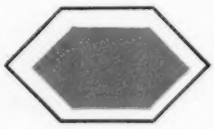
Squibb Quality—the Priceless Ingredient "NOCTEC" IS A SQUIBB TRADEMARK

unique derivative of *Rauwolfia canescens*

Harmonyl*

(Deserpidine, Abbott)





introduces a new degree of safety in major tranquilizing—antihypertensive therapy

Most significant: In extensive trials, Harmonyl has produced less mental and physical depression. And there are very few reports of the lethargy seen with many other rauwolfia preparations.

More than two years of clinical evaluation have proven Harmonyl a notably safe and effective agent in cases ranging from mild anxiety to major mental illnesses and in hypertension. Harmonyl exhibited significantly fewer and milder side effects in comparative studies with reserpine—while demonstrating effectiveness comparable to the most potent forms of rauwolfia.

Safety—plus marked clinical effectiveness

Harmonyl proved particularly effective, for example, in tranquilizing a group of 40 chronically ill, agitated senile patients.[1]

Of particular interest is the observation that patients became more lucid and alert on Harmonyl therapy. And there was a complete absence of side effects with Harmonyl—although a similar group on reserpine developed such side effects as anorexia, headache, bizarre dreams, shakes, nausea and vomiting.

Following another eight-month study of chronic, hospitalized mental patients, Ferguson[2] stated:

- Harmonyl benefited at least 15% more overactive patients and proved more potent in controlling aggression—requiring only one-half to two-thirds the dosage of reserpine.
- Patients experiencing side reactions on reserpine often were completely relieved when changed to Harmonyl.

Ferguson concluded: "*The most notable impressions were the absence of side effects and relatively rapid onset of action with Harmonyl.*"

Comparative studies have shown Harmonyl and reserpine about equal in hypotensive effect. The tranquilizing action of the two drugs also appeared similar—except that few cases of giddiness, vertigo, sense of detached existence or disturbed sleep were seen with Harmonyl.

Professional literature is available upon request. Harmonyl is supplied in 0.1-mg., 0.25-mg., and 1-mg. tablets. Abbott

References: 1. Communication to Abbott Laboratories, 1956. 2. Ferguson, J. T.: Comparison of Reserpine and Harmonyl in Psychiatric Patients: A Preliminary Report, Journal Lancet, 76:389, December, 1956. *Trademark

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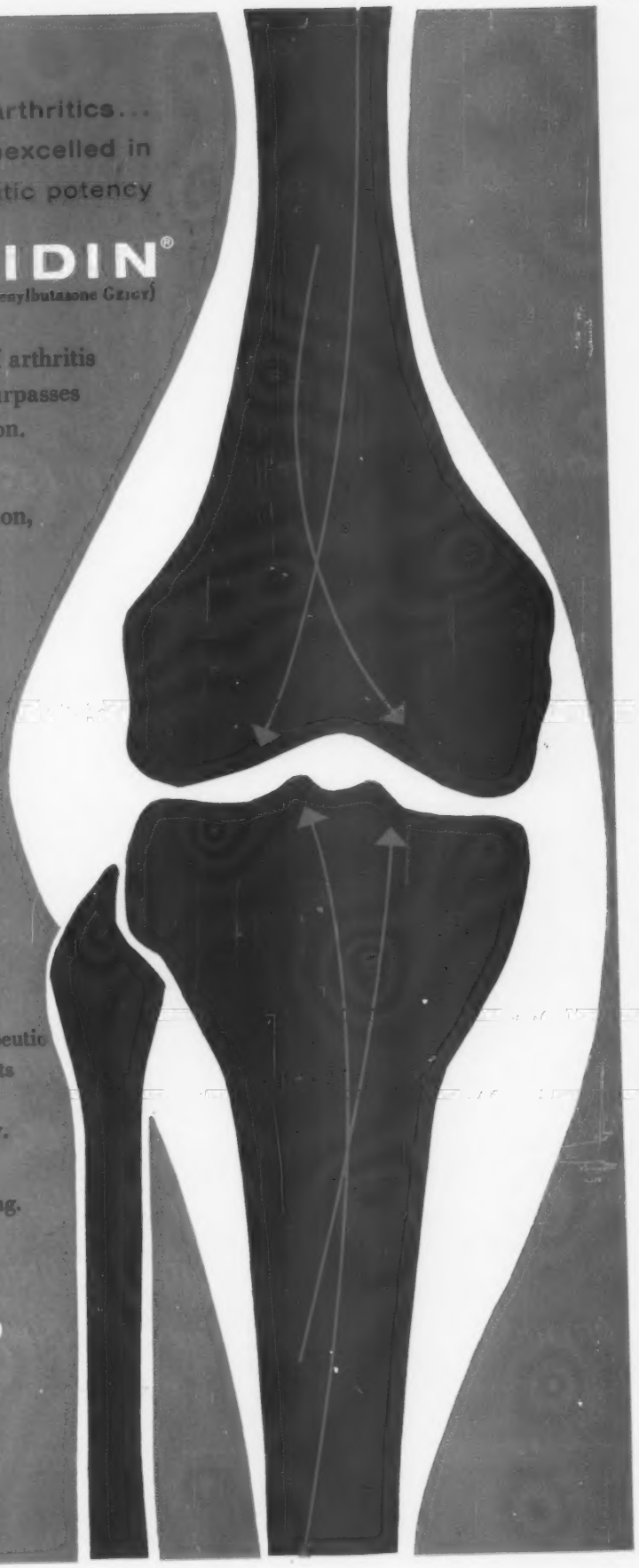

FOR SEVERE — INCLUDING MALIGNANT — HYPERTENSION

ECOLID is a powerful, orally effective ganglionic blocking agent. In some patients it has dramatically reversed the course of severe hypertension and prolonged their lives. ECOLID has been shown to produce a longer lasting, smoother and more consistent and predictable response than either pentolinium or hexamethonium. However, as with all ganglionic blocking agents, the patient must be carefully managed. Before instituting treatment with ECOLID, it is advised that the physician be thoroughly familiar with this drug's effects as well as side effects. Complete literature may be obtained from the Medical Service Division, CIBA, Summit, New Jersey.

SUPPLIED:
Tablets (Rotocotes), 25 mg. (ivory) and 50 mg. (pink).
New Form of Issue. 10 mg. (orange).

ECOLID® chloride (chlorisondamine chloride CIBA)
ROTOCOTES™ (compressed, dry-coated tablets CIBA)

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STERANE®*may not help him flush a covey, improve his aim or even help him bag a sitting duck... but* STERANE *can help steady your rheumatoid patient's hand and improve his position in almost any activity or profession by reducing joint pain, swelling and immobility. Provides prednisolone, the most active systemic corticoid, as white, scored 5 mg. tablets (bottles of 20 and 100) and pink, scored 1 mg. tablets (bottles of 100).*

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STRESSCAPS*

Treat stress by specific vitamin repletion

ONE OF A COMPLETE LINE OF VITAMIN PRODUCTS
Lederle
FORMULATED UNDER RIGID QUALITY CONTROL FOR YOUR PRESCRIPTION NEEDS

STRESSCAPS replenish the specific water-soluble vitamin losses sustained by patients under such stress situations as surgery, burns, fractures, trauma or shock.

The STRESSCAPS formulation is based on the most recent knowledge regarding the vitamin requirements of the human body under stress.

*Reg. U. S. Pat. Off.

dry-filled sealed capsules

Each Capsule Contains:	
Thiamine Mononitrate (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B_6)	2 mg.
Vitamin B_{12}	4 mcgm.
Folic Acid	1.5 mg.
Calcium Pantothenate	20 mg.
Vitamin K (Menadione)	2 mg.

Average Dose: 1-2 capsules daily.

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Effective bacteriostasis in bowel surgery

SULFATHALIDINE®

PHTHALYLSULFATHIAZOLE

SULFATHALIDINE, used before and after surgery, rapidly suppresses intestinal pathogens, particularly coliforms. This virtual "sterilization" of the G. I. tract minimizes the hazard of peritonitis and secondary infection.

With SULFATHALIDINE, the stool is soft (not fluid), flatus is minimal...tissue repair is thereby enhanced.

Absorption of SULFATHALIDINE is very low—bacteriostatic performance is concentrated where desired—in the gut.

Also supplied as palatable CREMOTHALIDINE® Suspension, each teaspoonful containing 1.0 Gm. of SULFATHALIDINE.

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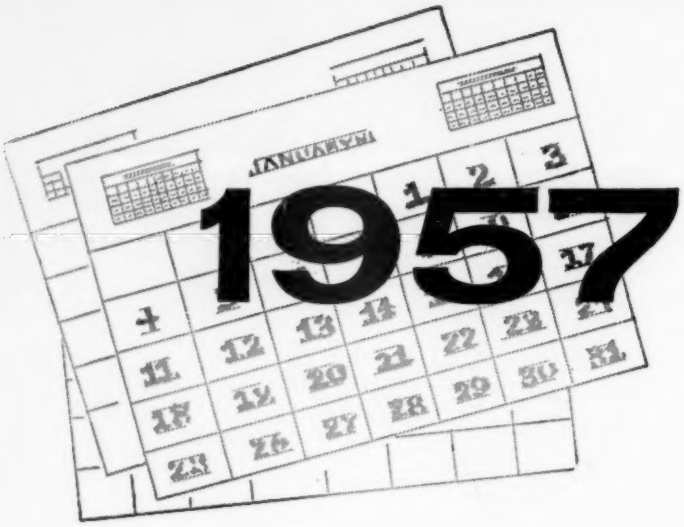
DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.



for faster and higher

now...the new phosphate

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the broad clinical spectrum of Sumycin

		Gram Negative Bacteria				
Large Viruses	Rickettsias	Proteus	Shigella	Salmonella	Coliforms	Hemophilus

Minimum adult dose: 1 capsule q.i.d.
Each Sumycin capsule contains the equivalent of 250 mg. tetracycline hydrochloride. Bottles of 16 and 100.

'Sumycin' is a Squibb trademark

SQUIBB *Squibb Quality—the Priceless Ingredient*

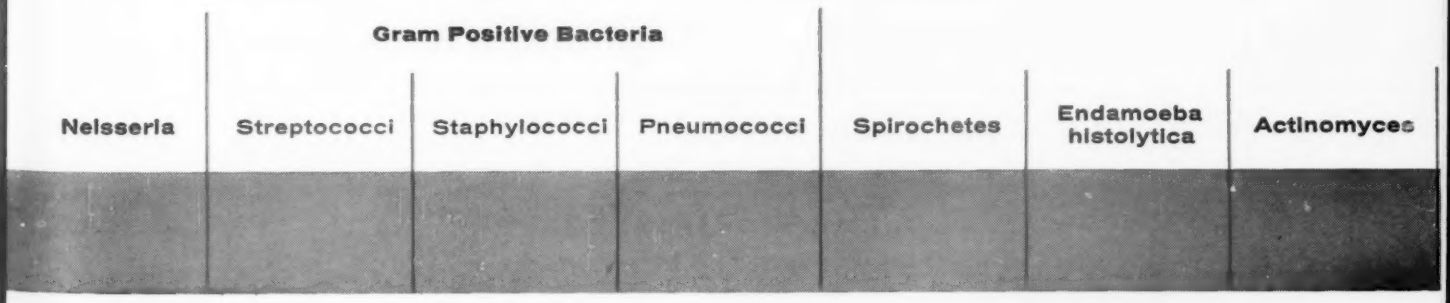
initial tetracycline blood levels

complex of tetracycline

YCIN

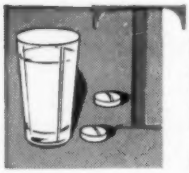
Squibb Tetracycline Phosphate Complex

against pathogenic organisms



- **SUMYCIN** the new **phosphate complex** of tetracycline
- **SUMYCIN** a **single** antibacterial antibiotic
- **SUMYCIN** a **well tolerated** antibiotic
- **SUMYCIN** a **true** broad spectrum antibiotic

In Angina Pectoris
More Comprehensive Action
Pentoxylon®



The patient with angina pectoris requires the comprehensive approach provided by the several actions of Pentoxylon. Each tablet combines the valuable *tranquilizing*, *fear-relieving*, *bradycrotic*, and *nonsoporific sedative* actions of Rauwiloid® (alseroxylon, 0.5 mg.), with the *long-lasting coronary vasodilating* effect of pentaerythritol tetranitrate (PETN, 10 mg.).

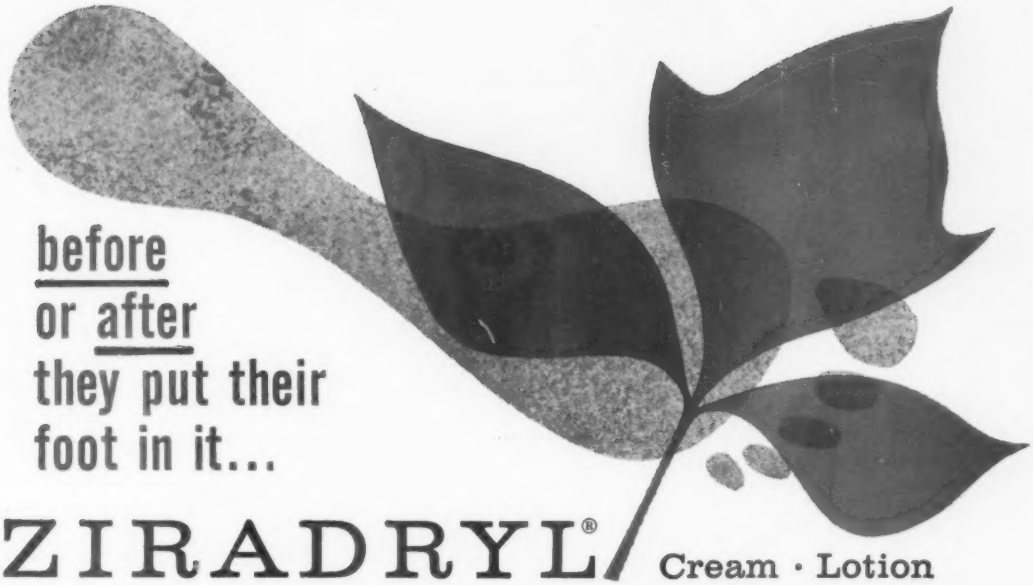
- **Reduces incidence and severity of attacks**
- **Increases exercise tolerance**
- **Reduces tachycardia**
- **Reduces anxiety, allays apprehension**
- **Reduces nitroglycerin need**
- **Lowers blood pressure only in hypertensives**
- **Produces demonstrable ECG improvement**

Dosage: one to two tablets q.i.d., before meals and on retiring

P.S. to stop the acute attack faster

Medihaler-Nitro™, the new self-propelled, measured-dose inhalation method delivers 1% octyl nitrite for instantaneous relief of acute anginal pain.

Riker
LOS ANGELES



before
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they put their
foot in it...

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Benadryl® Hydrochloride with Zirconium

- neutralizes toxins of poison ivy and of poison oak
- controls allergic process
- relieves itching

ZIRADRYL Cream is supplied in 1-ounce tubes.
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New Zylax

Tablets for Fast but Gentle Laxation

- RESULTS OVERNIGHT
- NO SIDE EFFECTS
- NO GRIPING OF CRAMPING
- SUGAR FREE
- CONVENIENT FOR ADULTS AND CHILDREN

Ingredients per tablet.

Active ingredient—Isatin (for the laxative effect of prunes)	5 mg.
Debittered brewer's dried yeast	160 mg.
Sodium carboxymethylcellulose	300 mg.

Please write for ZYLAX samples:

Literature available on other products:
Zymenol, a laxative emulsion containing healthful brewer's yeast
Zymelose Tablets with brewer's dried yeast and bulk-forming SCMC
BSP Liquid, the new product that helps prevent or heal bedsores

OTIS E. GLIDDEN & CO., Inc. Waukesha 27, Wisconsin

One of the safest, least toxic and most effectiv

therapeutic agents for many conditions in which th

weaker tranquilizers or sedatives are inadequat

CIBA

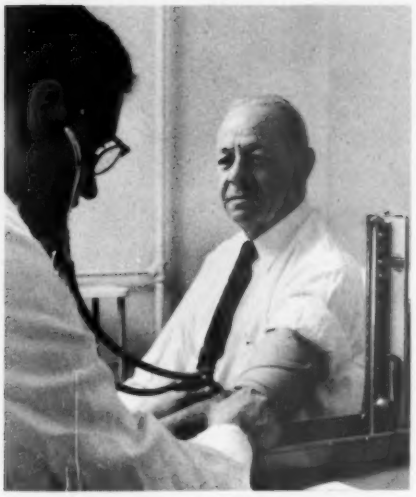
Serpasil

(reserpine CI

On the following pages you will find information on these aspects of Serpasil therapy:

The growing use of Serpasil in everyday practice

in hypertension



Serpasil® can always be considered first

BECAUSE *alone:* Serpasil successfully reduces blood pressure, slowly and safely, in about 70 per cent of cases of mild to moderate hypertension.[1]

BECAUSE *as a "primer":* Serpasil may be advantageously used to begin antihypertensive therapy, however severe the case, since it gently adjusts the patient to the physiologic setting of lower pressure.

BECAUSE *as a "background" agent throughout other therapy:* Serpasil permits lower dosage of the more potent antihypertensives needed for refractory cases, thus minimizing the incidence and severity of side effects.

USUAL DOSE: Initially, two 0.25-mg. tablets. After a week, daily dose should be reduced to 0.25 mg. or less for maintenance.

"...a useful agent for the treatment of certain types of hypertension....The action...was increased by combining it with [Apresoline]..."[2]

1. Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M. A. 51:417 (Dec.) 1955.
2. Winsor, T.: Ann. New York Acad. Sc. 59:61 (April 30) 1954.

in emotional disorders

Serpasil® provides true emotional control

In your daily practice there are undoubtedly many patients whose degree and type of emotional disturbance—characterized by overexcitation, anxiety and agitation—can *not* be adequately controlled with sedatives or weaker tranquilizers. These are the patients whom you can help most with once-a-day administration of Serpasil. For Serpasil actually sets up a "stress barrier" against anxiety and tension the patient would otherwise find intolerable. With Serpasil you can control the emotional turmoil of disturbed individuals; and because Serpasil is restricted to prescription use, control remains in your hands.

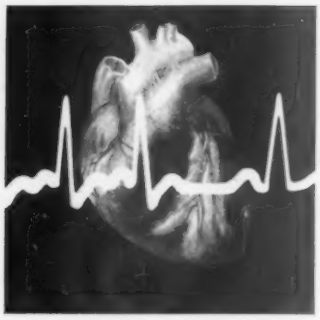
Although it is a first choice in hypertension, Serpasil does not significantly lower blood pressure in normotensive patients.

USUAL DOSE: Initial range is 0.1 mg. to 0.5 mg. (two 0.25-mg. tablets) daily. As little as 0.1 mg. is sufficient for maintenance in some patients. Serpasil can be given in a single daily dose.

"...relieves anxiety and irritability and calms the patient so effectively that because of this latter property alone, the drug should remain in the medicinal armamentarium."

Finnerty, F. A., Jr., and Sites, J. G.: Am. J. M. Sc. 229:379 (April) 1955.

in tachycardia



Serpasil® slows the rapid heart

Many patients can benefit from the heart-slowing action of Serpasil. Those in whom tachycardia is deleterious are helped by its unique bradycardic effect, for Serpasil prolongs diastole and allows more time for the myocardium to rest. Blood flow and cardiac efficiency are thus enhanced.

USUAL DOSE: 0.1 mg. to 0.5 mg. (two 0.25-mg. tablets) daily. After one or two weeks dose may be reduced.

"Reserpine [Serpasil] was found useful in relieving the tachycardia and emotional symptoms associated with cardiac arrhythmias, thyrotoxicosis, neurocirculatory asthenia, and even coronary heart disease."

Halprin, H.: J. M. Soc. New Jersey 52:616 (Dec.) 1955.

in acute hypertensive crises

Parenteral Serpasil

Serpasil can be used alone in hypertensive emergencies or as a background to more potent antihypertensive agents. Its antihypertensive action is prompt and well-tolerated.

USUAL DOSE: 2.5 mg. (1 ml.) intramuscularly. Additional intramuscular doses of 2.5 mg. may be given as necessary every 8 to 24 hours.

"...appears to be [a] treatment of choice for hypertensive crises."

Griffin, R. W., Stover, J. W., and Ford, R. V.: New England J. Med. 254:593 (March 29) 1956.

in alcoholism

Serpasil® relieves drink-inducing tension

As a part of long-term therapy, oral Serpasil helps the alcoholic "stay on the wagon" by relieving drink-inducing tension, making him more amenable to your counseling.

In acute alcoholism, delirium tremens can generally be controlled within 24 hours with parenteral Serpasil...without the addicting or soporific dangers of drugs such as paraldehyde.

USUAL DOSE: *Chronic phase:* two 0.25-mg. tablets or less daily. *Acute phase:* two 2.5-mg. parenteral doses (1 ml. each) 3 or more hours apart. Occasionally, repeat injections of 2.5 mg. every 4 to 6 hours may be necessary.

"...the tranquilizing and anxiety-relieving properties of this drug [Serpasil] offer the possibilities of its being extremely helpful for the long-term therapy of the chronic alcoholic."

Greenfield, A. R.: Am. Pract. & Digest Treat. 7:241 (Feb.) 1956.

in pediatric emotional problems

Serpasil Elixir benefits the "problem child"

Serpasil provides a shield against stress in the overreactive, tense, "problem child." Striking remissions have been observed in children with excessive crying, poor eating and sleeping patterns.

USUAL DOSE: 0.1 to 0.3 mg. daily (½ to 1½ teaspoons of Serpasil Elixir, 0.2 mg. per 4-ml. teaspoon).

"...provided dramatic relief in remitting the syndrome of irritability in 29 of the 32 cases studied..."

Talbot, M. W., Jr.: Ann. New York Acad. Sc. 61:188 (April 15) 1955.

in acute psychotic disturbances

Parenteral Serpasil

The family physician is often called to subdue and arrange for quick hospitalization of patients who suddenly experience violent psychotic episodes. With intramuscular Serpasil these patients are quickly tranquilized and rendered amenable to 'quiet' hospitalization.

USUAL DOSE: 5 mg. intramuscularly followed, if necessary, by another 5-mg. intramuscular dose in 90 minutes.

"It is now possible to discreetly manage acutely disturbed psychiatric patients by the prompt administration of adequate doses of reserpine (Serpasil)."

Ayd, F. J., Jr.: The Pharmacologic Management of Everyday Psychiatric Problems (A Scientific Exhibit). Presented at the Clinical Meeting of the American Medical Association, Boston, Mass., Nov. 29-Dec. 2, 1955.

Serpasil®: side effects and precautions

The side effects of Serpasil are characteristic of all rauwolfia preparations.

Although millions of patients have taken Serpasil over the past several years, very few serious side reactions have been reported. There have been no cases of blood dyscrasia, liver damage, addiction or withdrawal symptoms. When patients are properly selected and the lowest effective maintenance dose is established, the physician can prescribe Serpasil confidently, with little fear of untoward reactions.

Depression

Mental depression, which has developed in a small percentage of patients treated with rauwolfia, should be differentiated from the transient change in mood or physical fatigue that is experienced by almost everyone in the general population. It should also be distinguished from the lethargy experienced by some patients on rauwolfia therapy.

In the few cases in which mental depression does occur, there is some question as to whether or not it is a direct effect of rauwolfia. According to Mayo Clinic investigators,[1] the evidence indicates that rauwolfia *per se* does not cause depression, but rather that it unmasks an underlying susceptibility to depressive reactions. Kinross-Wright[2] states: "It is likely that depression will occur only in a predisposed individual or in one who is already mildly depressed." Ayd,[3] in a very recent paper, states: "That this drug may cause depression is uncertain. After reviewing a large number of so-called drug-induced depressions it appears that in some cases what was called depression was excessive tranquilization, while in the rest, the patients were depressed before the drug was started, and what the drug did was make the depression more apparent."

Whether or not it is an effect of rauwolfia, physicians and responsible members of the patient's family should be on the alert for the development of symptoms of depression, particularly in patients with a history of pre-existing depressive tendencies. Daily doses above 0.25 mg. are contraindicated in the latter group. On withdrawal of rauwolfia, depression usually disappears, but active treatment, including hospitalization for shock therapy, has been required in some cases.

Adjunctive use of mood-elevating agents such as Ritalin is often sufficient to reverse mild depressions or drug-induced lethargy.

Other side effects

In addition to lassitude or drowsiness, other mild side effects of Serpasil include occasional nasal stuffiness and increased frequency of defecation and/or looseness of stools. Rarely, anorexia, headache, bizarre dreams, nausea and dizziness occur. With parenteral Serpasil there is a possibility of marked hypotensive effect; therefore, the blood pressure should be taken before injection and the patient kept under observation for 5 or 6 hours thereafter. Because initial doses above 0.3 mg. tend to increase gastric secretion of hydrochloric acid, daily doses above 0.25 mg. are contraindicated in patients with a history of peptic ulcer and lower doses should be used with caution.

For further details on side effects and precautions, write Medical Service Division.

1. Litin, E. M., Faucett, F. L., and Achor, R. W. P.: Proc. Staff Meet., Mayo Clin. 31:233 (April 18) 1956.
2. Kinross-Wright, V.: Wisconsin M. J. 55:1073 (Oct.) 1956.
3. Ayd, F. J., Jr.: Presented at the Sesquicentennial Convention of The Medical Society of The State of New York, New York City, Feb. 18, 1957.

SUPPLIED:

TABLETS, 0.1 mg., 0.25 mg., 1 mg., 2 mg. and 4 mg.

ELIXIRS, 0.2 mg. and 1 mg. per 4-ml. teaspoon.

PARENTERAL SOLUTION: *Ampuls*, 2 ml., 2.5 mg. Serpasil per ml. *Multiple-dose Vials*, 10 ml., 2.5 mg. Serpasil per ml.

APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA)
RITALIN® hydrochloride (methylphenidate hydrochloride CIBA)

C I B A
SUMMIT, N. J.

2/2446MF

START WITH, OR CHANGE TO any dosage form—

without recalculation of dosage

digitaline nativelle®

oral · intramuscular · intravenous

If parenteral digitalization is imperative, or when a change in route of administration is required, DIGITALINE NATIVELLE eliminates the possible source of error associated with complex recalculation of dosage. And uncomfortable toxic symptoms occurring with dosage revision are also avoided, because DIGITALINE NATIVELLE requires *only* one change—to the dosage form of choice: oral, intramuscular or intravenous. All forms provide identical dosage schedules complete absorption, equal rate of onset.

Prescribe DIGITALINE NATIVELLE—the original pure crystalline digitoxin.

Consult your Physicians' Desk Reference for dosage information.

VARICK Pharmacal Company, Inc.
(Division of E. Fougera & Co., Inc.)
75 Varick Street, New York 13, N. Y.

"SUDDENLY I felt dizzy..."

Look out for the "little" strokes resulting from abnormal capillary fragility. Many cerebral accidents may be avoided if adequate amounts of capillary protective factors–hesperidin complex and ascorbic acid–are provided.[1]

The true character of the "little" strokes lies in their elusiveness—a sudden dizzy spell, temporary numbness of a hand, bizarre feeling of pain, or subtle personality change. Such symptoms are typical of little strokes and usually pass quickly, but they are likely to recur.[2,3]

Early recognition can gain vital therapeutic time. Hesper-C provides hesperidin complex and vitamin C essential for the protection of the capillaries to prevent further damage.

1. Gale, E. T., and Thewlis, M. W.: Geriatrics *8*:80, 1953. 2. Alvarez, W. C.: Geriatrics *10*:555, 1955. 3. Conference on Cerebral Vascular Disease, American Heart Association, Princeton, N. J., January, 1957.

Hesper-C

Available: As capsules—*and* NEW Hesper-C Liquid for your geriatric patients.

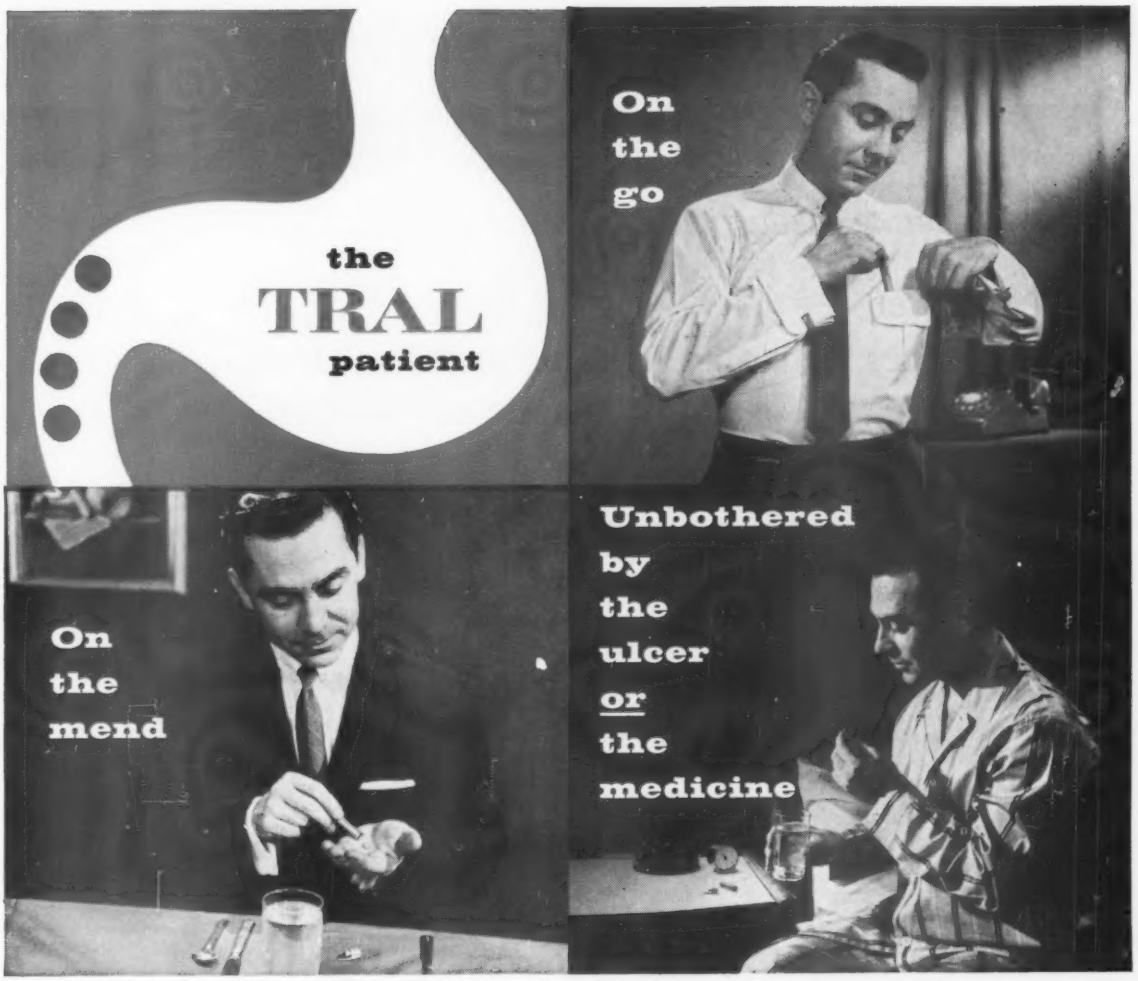
Provides: 100 mg. hesperidin complex plus 100 mg. ascorbic acid per capsule or teaspoonful (5 ml.) of syrup.

℞ 6 capsules or teaspoonfuls daily, or more. No toxicity or untoward effects have ever been reported even with massive doses.

Products of Original Research

THE NATIONAL DRUG COMPANY
Philadelphia 44, Pa.

H-1700/57



Marked selectivity in peptic ulcer therapy

With TRAL, your peptic ulcer patient receives selective anticholinergic action in the blocking of hypersecretion and hypermotility. Thus, the TRAL patient is rarely troubled by the side effects often resulting from unwanted anticholinergic action outside the gastrointestinal tract.

(In more than 1,000 clinical cases,† blurring of vision, urinary retention, palpitation and constipation—limiting factors in anticholinergic therapy—were rarely encountered. The only reaction which was at all common was dryness of the mouth, and this was mild in most instances.)

In motility studies, TRAL produced clear-cut inhibition of intestinal motility without paralysis in doses of from 25 to 100 mg. Anacidity or definite reduction of free acidity developed for various periods of time in 92% of TRAL patients in one clinical study group.

This new drug is supplied as Filmtab TRAL *(25 mg.) and as Filmtab* TRAL *(25 mg.) with Phenobarbital (15 mg.), both in bottles of 100 tablets.*

Abbott Filmtab® TRAL*

(Hexocyclium Methylsulfate, Abbott)

† Complete literature available on request.

*TRAL—TRADEMARK. ®FILMTAB—FILM-SEALED TABLETS, ABBOTT; PAT. APPLIED FOR.

706171

FOLIC ACID

Primary agent in megaloblastic anemia of pregnancy and infancy, achrestic anemia and sprue. Reinforces B_{12} in other macrocytic anemias.

NON-INHIBITORY INTRINSIC FACTOR

Essential to the assimilation of oral B_{12} in pernicious and other macrocytic anemias.

IRON

Primary agent in microcytic anemia due to iron deficiency. Is more active when vitamin C is present.

VITAMIN C

Potentiates iron in microcytic anemia and folic acid in macrocytic anemias.

VITAMIN B_{12}

Primary agent in pernicious and nutritional macrocytic anemia, but is not assimilated orally without intrinsic factor. Reinforces folic acid in other macrocytic anemias.

Designed for hematinic potentiation

No wasted dosage with PRONEMIA—each factor is present in the specific amounts required for *true hematinic potentiation.* Only one capsule daily for full oral therapy in any treatable anemia. (When divided dosage of this formula is preferred prescribe PERIHEMIN* Hematinic, 3 capsules daily).

PRONEMIA*

HEMATINIC LEDERLE

Each PRONEMIA *Capsule contains:*

Vitamin B_{12} with Intrinsic Factor Concentrate	1 U.S.P. Oral Unit
Vitamin B_{12} (additional)	15 mcgm.
Powdered Stomach	200 mg.
Ferrous Sulfate Exsiccated	400 mg.
Ascorbic Acid (C)	150 mg.
Folic Acid	4 mg.

Lederle LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

*Reg. U. S. Pat. Off.

NEOBON®

TO FIGHT THE INROADS OF AGE

Current opinion stresses the importance of early recognition of the undesirable effects of aging, and adequate metabolic support of the body's fight against them.[1] NEOBON, by providing 4 factors PLUS 1, corrects all 5 of the recognized treatable causes of aging.

Gonadal Hormone Decline—NEOBON'S daily dose of 3 mg. Methyltestosterone and 0.018 mg. Ethinyl Estradiol offsets it.

Hematinic Deficiencies—NEOBON combats nutritional anemia and iron deficiency with essential hematinic factors.

Digestive Enzyme Deficiency—NEOBON supplies pepsin and pancreatin to insure proper absorption and utilization of foods—despite digestive "let-down" of aging.

Nutritional Inadequacy—NEOBON'S complete combination of essential minerals and vitamins replaces deficiencies inherent in the restricted diets of the aging.

PLUS—NEOBON'S new lysine, the amino acid that lifts low value vegetable proteins to the high grade quality found in meat and eggs.

NEOBON in bottles of 60 soft, soluble capsules; prescription only.

1. Klemme, H. L.: Clin. Med., October, 1956.

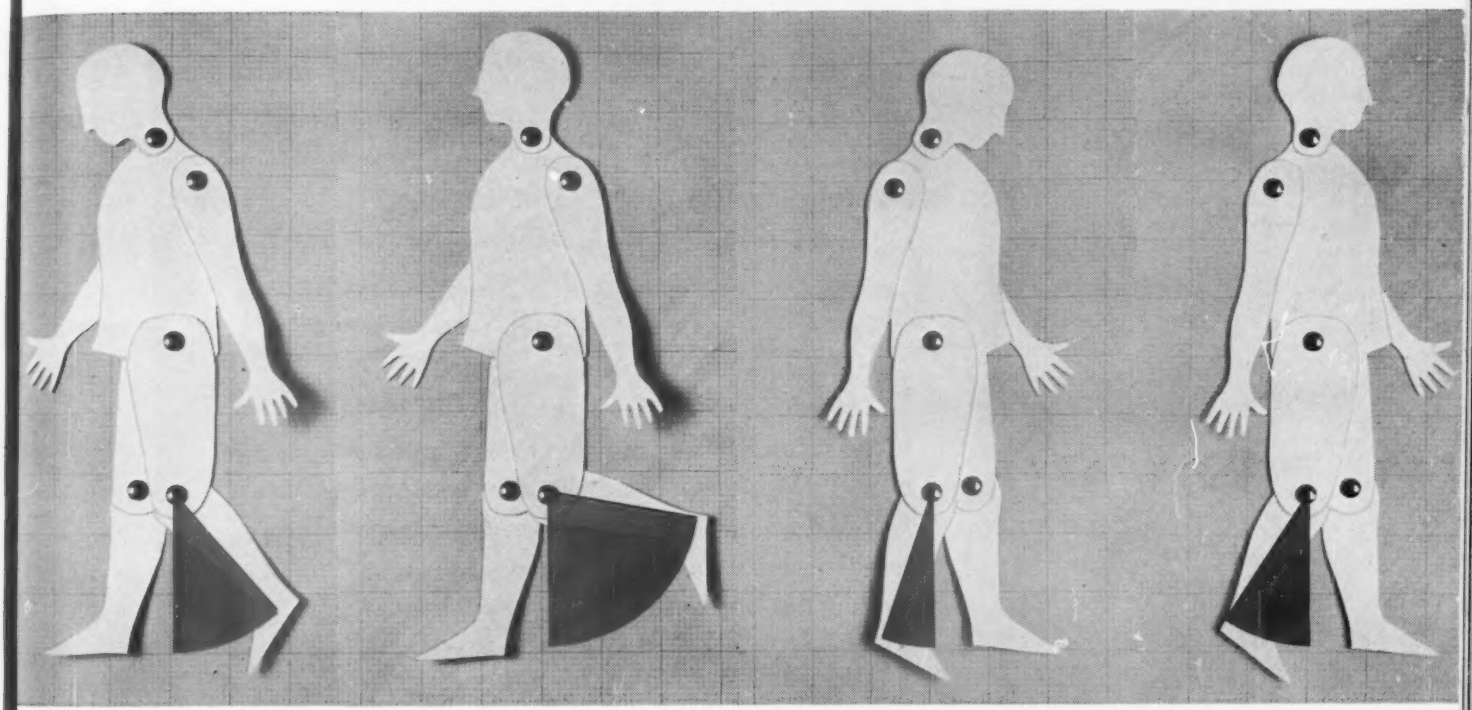
NEW NEOBON® LIQUID, *a geriatric tonic providing gonadal and thyroid supplementation, improved carbohydrate and protein utilization, hematinic action, and mild antidepressant effect.*

In 16 oz. bottles; prescription only.

PEACE of mind ATARAX® ROERIG Chicago 11, Illinois

Effective muscle relaxation for your patients with rheumatic, neurologic and similar conditions.

Patient, male, age 40, spastic diplegia; physiotherapy and massage previously ineffective. When Tolseram was administered, the following improvement was seen within a month:



left knee, active: from 42° range to 80° range (nearly 100% increase)

right knee, active: from 20° range to 34° range (70% increase)*

*FROM ENGLER, M.: J. MENT. SCI. 101:391 (APRIL) 1955.

TOLSERAM

Squibb Mephenesin Carbamate

Tolseram Tablets, 0.5 Gm., bottles of 100, 1000; Tolseram Suspension, 1.0 Gm. per 5 cc. tsp., pints and gallons. **Adult dosage:** 4 to 6 Tablets or 2 to 3 tsp. Suspension 3 to 5 times daily.

Also available:

Tolserol (Squibb Mephenesin) Tablets, 0.25 Gm. and 0.5 Gm., bottles of 100, 1000; Elixir, 0.5 Gm. per 5 cc. tsp., pints and gallons; Solution, 20 mg. per cc., 50 and 100 cc. ampuls. Tolserol with Codeine Tablets (0.5 Gm. Tolserol with 1/8 gr. codeine), bottles of 100, 1000.

SQUIBB SQUIBB QUALITY—THE PRICELESS INGREDIENT

Rauwiloid®

A Better Antihypertensive

"We prefer to use alseroxylon (Rauwiloid)

since it is less likely to produce excessive fatigue and weakness than does reserpine."[1] Up to 80% of patients with mild labile hypertension and many with more severe forms are controlled with Rauwiloid alone.

1. Moyer, J.H.: J. Louisiana M. Soc. *108*:231 (July) 1956.

A Better Tranquilizer, too

"...relief from anxiety resulted in generally increased intellectual and psychomotor efficiency with a few exceptions."[2] Rauwiloid is outstanding for its *nonsoporific* sedative action in a long list of unrelated diseases not necessarily associated with hypertension but burdened by psychic overlay.

2. Wright, W.T., Jr., et al.: J. Kansas M. Soc. *57*:410 (July) 1956.

Dosage: Merely two 2 mg. tablets at bedtime. After full effect one tablet suffices.

Best first step when more potent drugs are needed

Rauwiloid is recognized as basal medication in all grades and types of hypertension. In combination with more potent agents it proves synergistic or potentiating, making smaller dosage effective and freer from side actions.

Rauwiloid® + Veriloid®

In moderate to severe hypertension this single-tablet combination permits long-term therapy with dependably stable response. Each tablet contains 1 mg. Rauwiloid and 3 mg. Veriloid. Initial dose, 1 tablet t.i.d., p.c.

Rauwiloid® + Hexamethonium

In severe, otherwise intractable hypertension this single-tablet combination provides smoother, less erratic response to hexamethonium. Each tablet contains 1 mg. Rauwiloid and 250 mg. hexamethonium chloride dihydrate. Initial dose, ½ tablet q.i.d.

Riker LOS ANGELES

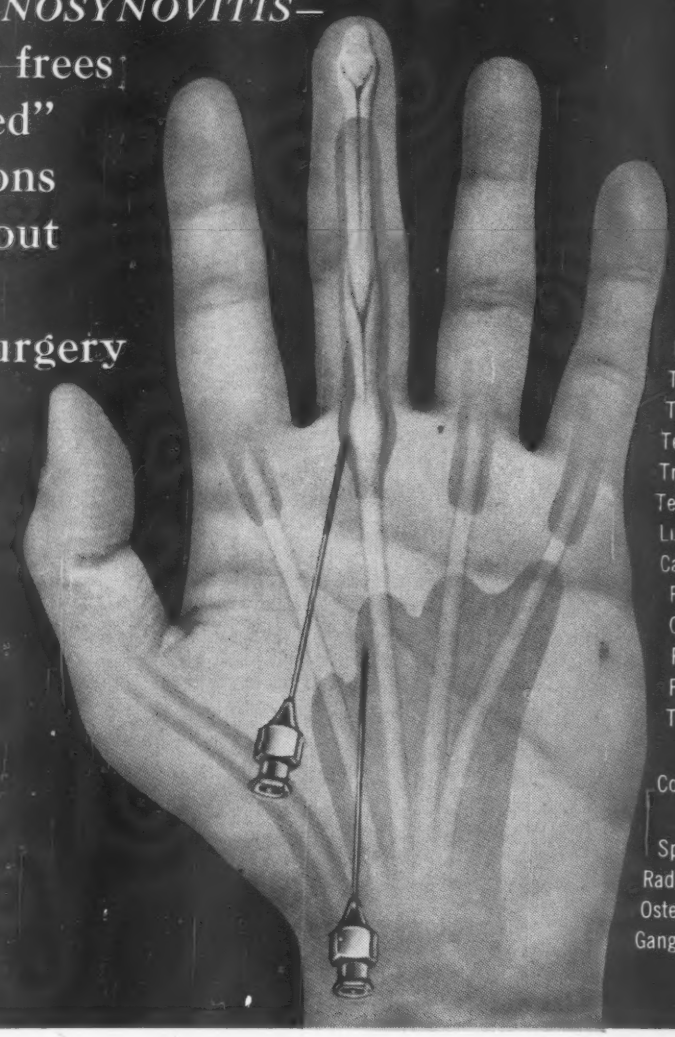
NEW

HYDELTRA®-T.B.A.

(Prednisolone *tertiary*-butylacetate, Merck)

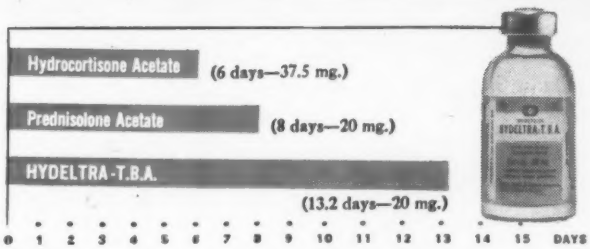
for relief that lasts—longer

in *TENOSYNOVITIS*—
often frees
"locked"
tendons
without
need
for surgery



- Osteoarthritis
- Rheumatoid arthritis
- Acute gouty arthritis
- Bursitis
- Tendinitis
- Trigger finger
- Tenosynovitis
- Trigger points
- Tennis elbow
- Lumbosacral strain
- Capsulitis
- Frozen shoulder
- Coccydynia
- Rheumatoid nodules
- Fibrositis
- Tensor fascia lata syndrome
- Collateral ligament strains
- Sprains
- Radiculitis
- Osteochondritis
- Ganglia

Anti-inflammatory effect lasts longer than that provided by any other steroid ester



Dosage: the usual intra-articular, intra-bursal or soft tissue dose ranges from 20 to 30 mg. depending on location and extent of pathology.

Supplied: Suspension 'HYDELTRA'-T.B.A.—20 mg./cc. of prednisolone *tertiary*-butylacetate, in 5-cc. vials.

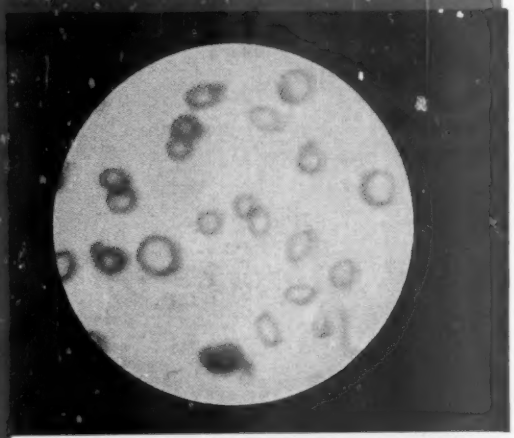
MSD

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC.
PHILADELPHIA 1, PA.

let the blood picture

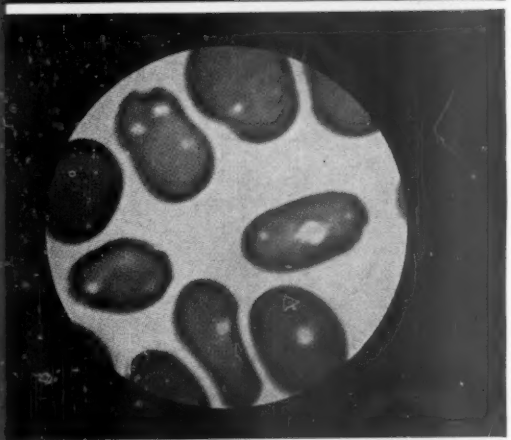
MICROCYTIC HYPOCHROMIC ANEMIA

RBC smaller than normal . . . low color index. An iron deficiency state found in bleeding peptic ulcer, bleeding hemorrhoids, or metrorrhagia. Also, the most common pregnancy anemia. HEPTUNA PLUS supplies iron, the specific for these anemias, as well as vitamins, and other factors. In pregnancy, OBRON HEMATINIC provides iron, plus full prenatal supplementation.



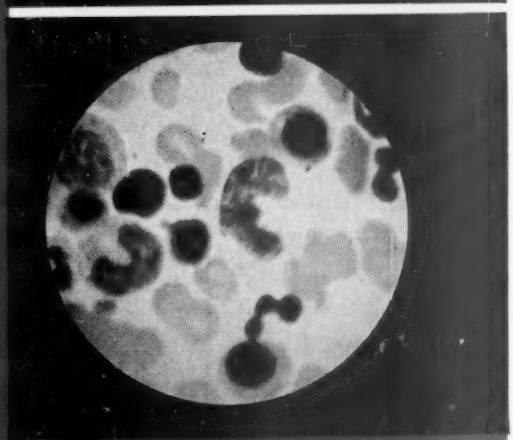
MACROCYTIC ANEMIA

All these show deficiency of anti-anemic principle. Macrocytosis is characteristic . . . hemoglobin decreased, color index high. Found in cirrhosis of the liver, intestinal obstruction, carcinoma, pernicious anemia of pregnancy, etc. Intrinsic factor/B_{12} concentrate, plus folic acid, present in ROETINIC are effective erythrocyte maturation agents.



PERNICIOUS ANEMIA

Macrocytosis . . . characterized by achlorhydria and other GI and neurologic disturbances. RBC count may be less than 10% of normal . . . high color index. Administration of intrinsic factor/B_{12} concentrate formulated in ROETINIC produces a satisfactory reticulocyte response.



decide

WHEN MORE THAN A HEMATINIC IS REQUIRED, HEPTUNA PLUS supplies iron, vitamins and trace minerals. The formula, liberal in iron, folic acid and B_{12} content, will correct most microcytic anemias, of course. But more than that, HEPTUNA PLUS is widely useful in the commonest anemia of all: anemia complicated by other nutritional deficiencies.

In moderate conditions, 1 to 3 capsules daily. In severe cases, 4 or more daily. Supplied: Bottles of 100 soft, soluble capsules.

HEPTUNA® PLUS

FOR ALL TREATABLE ANEMIAS, ROETINIC is formulated with the new intrinsic factor/B_{12} concentrate and high folic and ascorbic acids content. Aimed primarily at the more complicated macrocytic anemias of faulty hemopoiesis and those normocytic anemias due to hemolysis.

Therapeutic dosage is just one capsule daily. Supplied: Bottles of 30 and 100 soft, soluble capsules.

ROETINIC®

FOR THE ANEMIAS OF PREGNANCY, OBRON HEMATINIC is a complete hematinic and prenatal supplement. Formula includes high iron content plus calcium, folic acid, B_{12}, eight other minerals, eight essential vitamins.

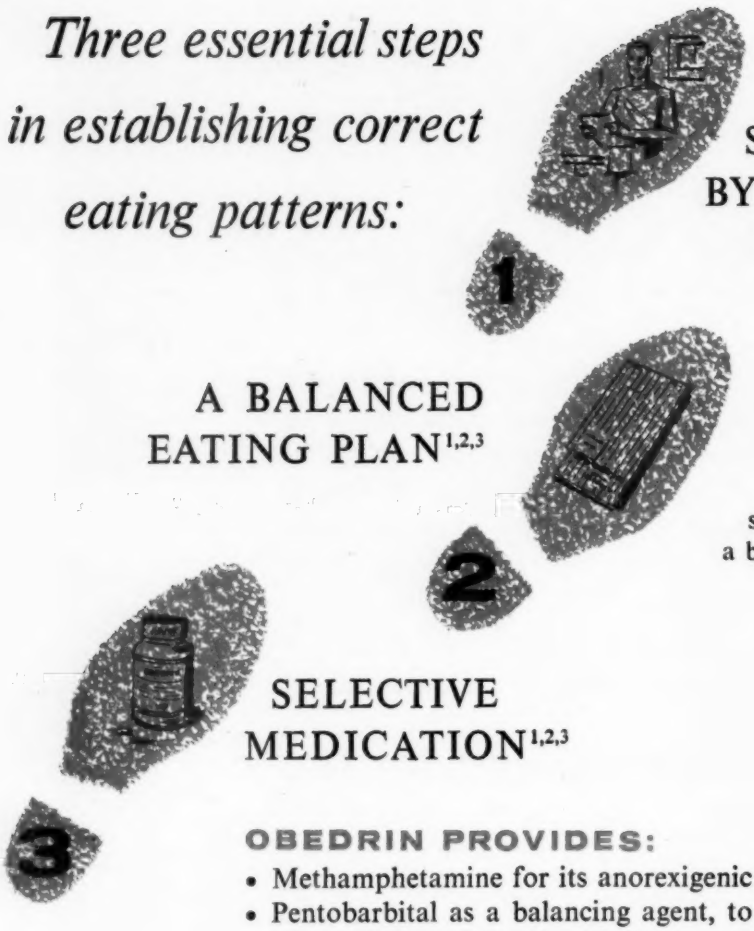
Dosage as required, usually two capsules daily. Supplied: Bottles of 100 soft, soluble capsules.

OBRON® HEMATINIC

ROERIG

CHICAGO 11, ILLINOIS. PEACE of mind ATARAX®

Three essential steps in establishing correct eating patterns:



SUPERVISION BY THE PHYSICIAN[1,2,3]

A BALANCED EATING PLAN[1,2,3]

SELECTIVE MEDICATION[1,2,3]

In the development and maintenance of good eating habits, there are three essentials: support and supervision by the physician, a balanced eating plan, and selective medication.[1,2,3]

OBEDRIN PROVIDES:

- Methamphetamine for its anorexigenic and mood-lifting effects.
- Pentobarbital as a balancing agent, to guard against excitation.
- Vitamins B_1 and B_2 plus niacin to supplement the diet.
- Ascorbic acid to aid in the mobilization of tissue fluids.

Since Obedrin contains no artificial bulk, the hazards of impaction are avoided. The 60-10-70 Basic Plan provides for a balanced food intake, with sufficient protein and roughage.

1. Eisfelder, H.W.: Am. Pract. & Dig. Treat. *5*:778 (Oct. 1954).
2. Freed, S.C.: G.P. *7*:63 (1953).
3. Sherman, R.J.: Medical Times, *82*:107 (Feb. 1954).

Obedrin®

and the 60-10-70 Basic Plan

FORMULA:

Semoxydrine HCl (Methamphetamine HCl) 5 mg.; Pentobarbital 20 mg.; Ascorbic acid 100 mg.; Thiamine mononitrate 0.5 mg.; Riboflavin 1 mg.; Niacin 5 mg.

Write for 60-10-70 Menu pads, weight charts and clinical supply of Obedrin.

THE S. E. MASSENGILL COMPANY

BRISTOL, TENNESSEE

NEW YORK • KANSAS CITY • SAN FRANCISCO

new assurance

for the aged with

herpes zoster

...to promote prompt recovery

and greater freedom from

postherpetic neuralgia.

PROTAMIDE®

Sherman Laboratories

Detroit 11, Michigan

Supplied: Boxes of ten 1.5 cc. ampuls

highly effective—clinically proved

Sigmamycin*

OLEANDOMYCIN TETRACYCLINE

provides added certainty in antibiotic therapy particularly for that 90% of the patient population treated in home or office...

Multi-spectrum synergistically strengthened SIGMAMYCIN provides the antimicrobial spectrum of tetracycline extended and potentiated with oleandomycin to include even those strains of staphylococci and certain other pathogens resistant to other antibiotics.

Supplied: SIGMAMYCIN CAPSULES—250 mg. (oleandomycin 83 mg., tetracycline 167 mg.), bottles of 16 and 100; 100 mg. (oleandomycin 33 mg., tetracycline 67 mg.), bottles of 25 and 100. SIGMAMYCIN FOR ORAL SUSPENSION—1.5 Gm., 125 mg. per 5 cc. teaspoonful (oleandomycin 42 mg., tetracycline 83 mg.), mint flavored, bottles of 2 oz.

*Trademark

Pfizer PFIZER LABORATORIES, Brooklyn 6, N. Y.
Division, Chas. Pfizer & Co., Inc.
World leader in antibiotic development and production

clinically established*

FLEXIN®

Enteric coated • plain

in Low back pain

* see other side

flexin®

Zoxazolamine*

consistently effective in low back pain

"...Of 90 patients with low back pain and other muscular conditions... 67 (74 per cent) showed a good response...."[1]

"...17 of...20 patients with post-traumatic muscle spasm of the low back had excellent or good responses."[2]

"In acute and chronic recurrent low back syndrome, seven of eight patients showed visible objective improvement."[3]

Bibliography

(1) Johnson, H. J., Jr.: To be published. (2) Wallace, S. L.: To be published. (3) Settel, E.: Am. Pract. & Digest Treat. 8:443, 1957.

How Supplied

Pink, Enteric Coated tablets (250 mg.), bottles of 36.
Yellow, scored tablets (250 mg.), bottles of 50.

*U.S. Patent Pending

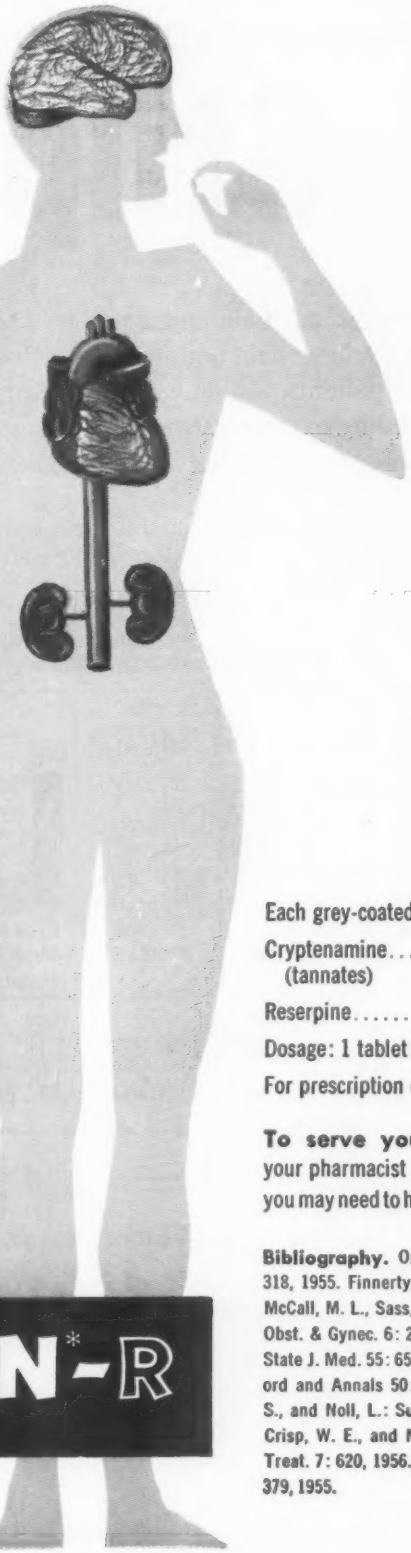
McNEIL

Laboratories, Inc.
Philadelphia 32, Pa.

11087

HYPERTENSION

"ACTING IN CONCERT"†



to treat

the hypertensive patient

as a whole

Unitensen-R combines cryptenamine and reserpine which "act in concert" to control the entire syndrome of essential hypertension.

Cryptenamine dependably lowers blood pressure, and improves cerebral and renal circulation. It also increases cardiac efficiency, and may arrest the progress of vascular damage.

Reserpine raises the threshold of emotional response and stifles neurogenic aggravation of the disease.

Given together, cryptenamine and reserpine produce a far better therapeutic effect than when given separately. And successful therapy is usually maintained with dosages well below those producing side effects.

†Cohen, B. M.; Cross, E. B., and Johnson W.: Am. Prac. & Digest Treat. 6: 1030, 1955.

UNITENSEN*-R

*T.M., Reg. U.S. Pat. Off.

IRWIN, NEISLER & COMPANY

DECATUR, ILLINOIS

Each grey-coated Unitensen-R tablet contains:

Cryptenamine (tannates) ..... 1.0 mg.

Reserpine ..... 0.1 mg.

Dosage: 1 tablet t.i.d.

For prescription economy, prescribe in 50's.

To serve your patients today—call your pharmacist for any additional information you may need to help you prescribe Unitensen-R.

Bibliography. Orgain, E. S.: Postgrad. Med. 17: 318, 1955. Finnerty, F. A.: Am. J. Med. 17: 629, 1954. McCall, M. L., Sass, D. K., Wagstaff, C., and Cutler, J.: Obst. & Gynec. 6: 297, 1955. Cohen, B. M.: New York State J. Med. 55: 653, 1955. LaBarbera, J. F.: Med. Record and Annals 50: 242, 1956. Voskian, J.; Assali, N. S., and Noll, L.: Surg., Gynec. & Obst. 102: 37, 1956. Crisp, W. E., and McCall, M. L.: Am. Prac. & Digest Treat. 7: 620, 1956. Finnerty F. A.: Am. J. M. Sc. 229: 379, 1955.

orally...intravenously

palliative of choice

in prostatic carcinoma

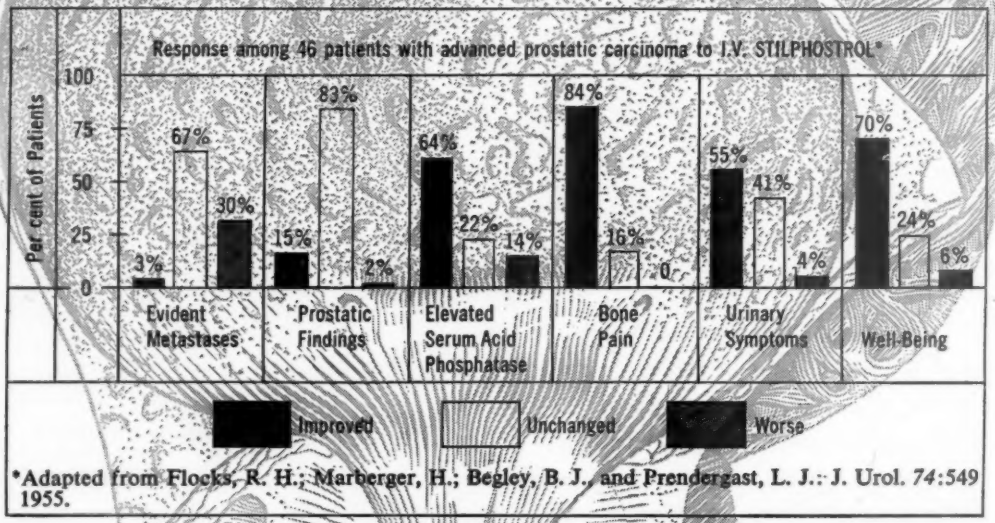
Stilphostrol®

Diethylstilbestrol Diphosphate, AMES
Tablets · Ampuls

Initially or as maintenance after I.V. therapy, well-tolerated STILPHOSTROL Tablets relieve pain and increase well-being in nonhospitalized as well as hospitalized patients. Palliative action is often obtainable even in patients no longer responding to other estrogens.

See your 1957 P D R for oral and intravenous dosage and administration, or write for literature.

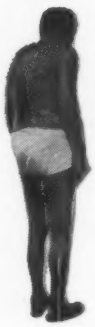
Packaging: STILPHOSTROL Tablets, diethylstilbestrol diphosphate 50 mg., bottles of 50. STILPHOSTROL Ampuls, 5 cc., containing diethylstilbestrol diphosphate 0.25 Gm. as a solution of the sodium salt, boxes of 20.



*Adapted from Flocks, R. H.; Marberger, H.; Begley, B. J., and Prendergast, L. J.: J. Urol. *74*:549 1955.

AMES COMPANY, INC. · ELKHART, INDIANA

84987



NOW—EFFECTIVE STEROID HORMONE THERAPY OF RHEUMATIC AFFECTIONS WITH GREATER SAFETY AND ECONOMY

PABALATE'-HC

Robins

Pabalate with Hydrocortisone

Clinical evidence indicates that, in Pabalate-HC, the synergistic antirheumatoid effects of hydrocortisone, salicylate, para-aminobenzoate, and ascorbic acid achieve satisfactory remission of symptoms in *up to 85% of cases studied*

—with a much higher degree of safety

—even when therapy is maintained for long periods

—at significant economy for the patient

Each tablet of Pabalate-HC contains 2.5 mg. of hydrocortisone—50% more potent than cortisone, yet not more toxic.

FORMULA

each tablet:

drocortisone (alcohol)	2.5 mg.
tassium salicylate	0.3 Gm.
tassium para-aminobenzoate	0.3 Gm.
corbic acid	50.0 mg.

DSAGE: Two tablets four times daily.
ditional information on request.

AVAILABLE FOR YOUR PRESCRIPTION NOW

A. H. ROBINS CO., INC. RICHMOND 20, VIRGINIA
Ethical Pharmaceuticals of Merit since 1878

designed to

control anxiety

in Arthritis, Asthma, Allergic Dermatoses

with

lower corticoid dosage

the original tranquilizer-corticoid

Ataraxoid*

prednisolone and hydroxyzine

provides the emotional tranquilizer, ATARAX® (hydroxyzine) and the preferred corticoid, STERANE® (prednisolone) • control of emotional factors by tranquilization enhances response to the corticoid for greater clinical improvement • often permits substantial reductions in corticoid dosage, accompanied by reduction of hormonal side effects • confirmed by marked success in 95% of 1095 cases of varied corticoid indications[1]

ATARAXOID *now written as* **Ataraxoid 5.0**

5 mg. prednisolone, 10 mg. hydroxyzine hydrochloride, in green, scored tablets. Bottles of 30 and 100.

and now available as **NEW Ataraxoid 2.5**

2.5 mg. prednisolone, 10 mg. hydroxyzine hydrochloride, in blue, scored tablets. Bottles of 30 and 100.

and **NEW Ataraxoid 1.0**

1.0 mg. prednisolone, 10 mg. hydroxyzine hydrochloride, in orchid, scored tablets. Bottles of 100.

formerly **Ataraxoid**
NOW written **Ataraxoid 5.0**

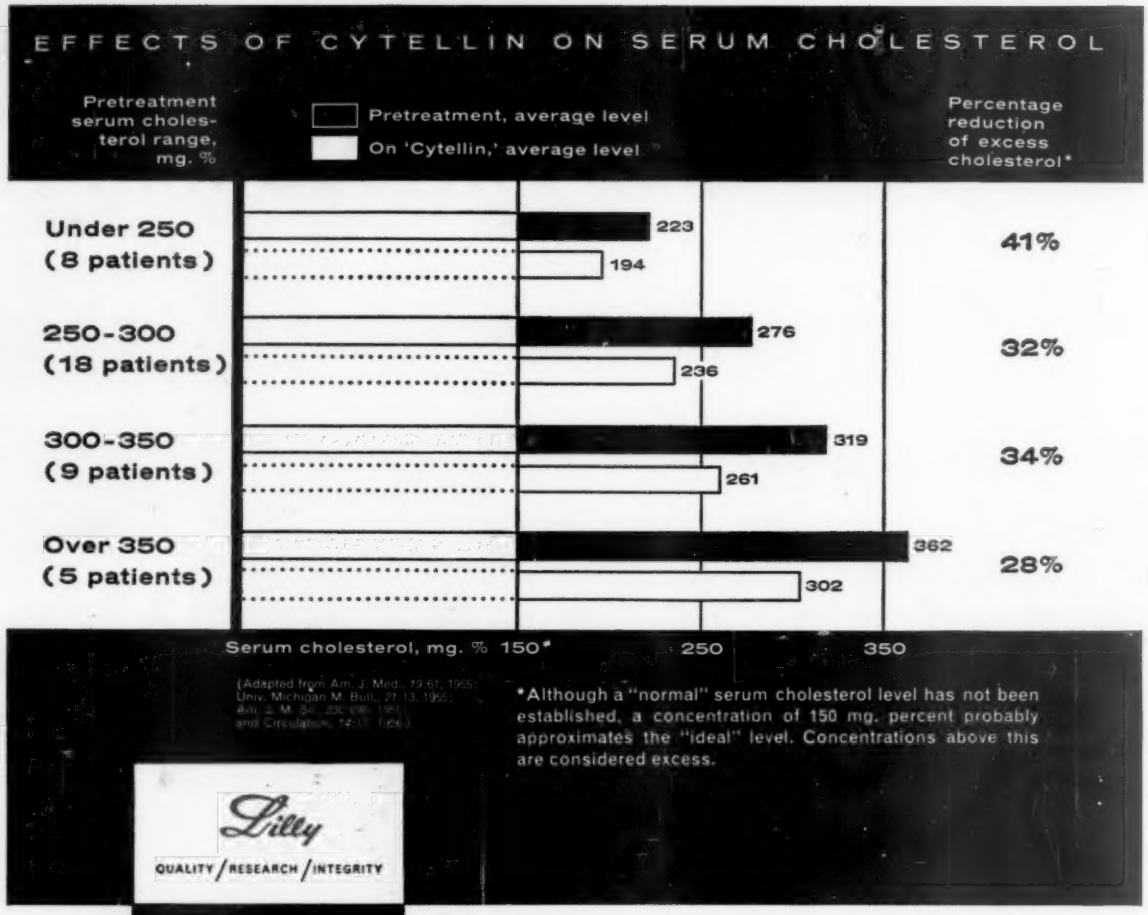
advantages: (1) greater flexibility of dosage (2) effective tranquilization permits lower corticoid dosage

1. Personal communications

*Trademark

PFIZER LABORATORIES *Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York*

Pfizer



Lilly
QUALITY / RESEARCH / INTEGRITY

reduces
elevated serum cholesterol

CYTELLIN

(Sitosterols, Lilly)

'Cytellin' reduces the absorption of dietary cholesterol and the reabsorption of endogenous cholesterol excreted in the bile. Severe dietary restrictions are not necessary to obtain a significant decline in serum cholesterol level. For a majority of patients, 'Cytellin' provides the most rational and practical therapy available.

In addition to lowering hypercholesteremia, 'Cytellin' has been reported to effect reductions in C/P ratio, S_f10-100 lipoproteins, and beta lipoproteins.

May we send more complete information?

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U. S. A.

773027

"Arteriosclerosis of the central nervous system is the commonest cause of vertigo that we see. . . . It is usually mild, is often positional and responds poorly to treatment. Dramamine and sedation are often beneficial. . . ."

Lewis, M. L., Jr.: The Problem of the Dizzy Patient, New Orleans M. & S. J. *104*:161 (Oct.) 1951.

Dizziness in the elderly patient with arteriosclerosis

for dramatic results

Dramamine® SEARLE

Brand of Dimenhydrinate

V stands for— • **greater antibiotic absorption** • **earlier therapeutic blood levels** • **faster broad-spectrum action.** ACHROMYCIN V Capsules are the new, rapid-acting, oral form of ACHROMYCIN* Tetracycline—offering your patients, on the average, twice the antibiotic absorption in half the time required by older preparations.

Susceptibility factors play an important part in the occurrence and spread of athlete's foot. With the advent of warm weather, individuals who have had the disease are prone to exhibit recurrences or reinfection. Frequently, this can be prevented by the continuous prophylactic use of Desenex preparations.

Desenex®

OINTMENT and SOLUTION

Buffered at pH 6.5

POWDER

relieves itching
stops fungal growth
prevents recurrence

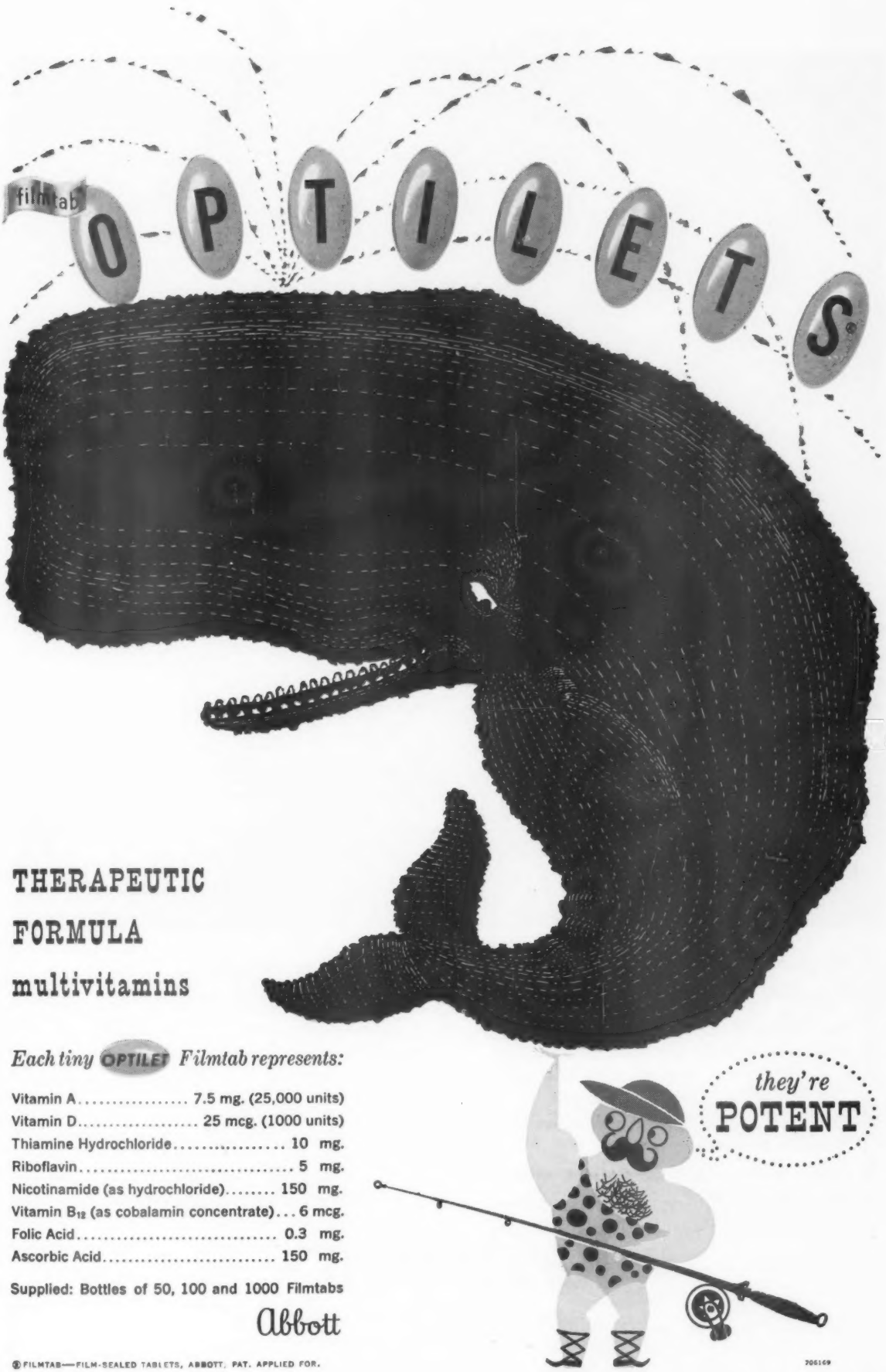
Maltbie

For most effective and convenient therapy and continuing prophylaxis, use Desenex as follows: **AT NIGHT** the Ointment (zincundecate)—1 oz. tubes and 1 lb. jars. **DURING THE DAY** the Powder (zincundecate)—1½ oz. and 1 lb. containers. **AFTER EVERY FOOT BATH** the Solution (undecylenic acid)—2 fl. oz. and 1 pt. bottles. The Solution should not be used on broken skin. In otomycosis, Desenex solution or ointment.

Write to Professional Service Department for free sample supply.

MALTBIE LABORATORIES DIVISION • WALLACE & TIERNAN, INC. • Belleville 9, N.J.

FD-75



THERAPEUTIC FORMULA multivitamins

Each tiny OPTILET *Filmtab represents:*

Vitamin A	7.5 mg. (25,000 units)
Vitamin D	25 mcg. (1000 units)
Thiamine Hydrochloride	10 mg.
Riboflavin	5 mg.
Nicotinamide (as hydrochloride)	150 mg.
Vitamin B_{12} (as cobalamin concentrate)	6 mcg.
Folic Acid	0.3 mg.
Ascorbic Acid	150 mg.

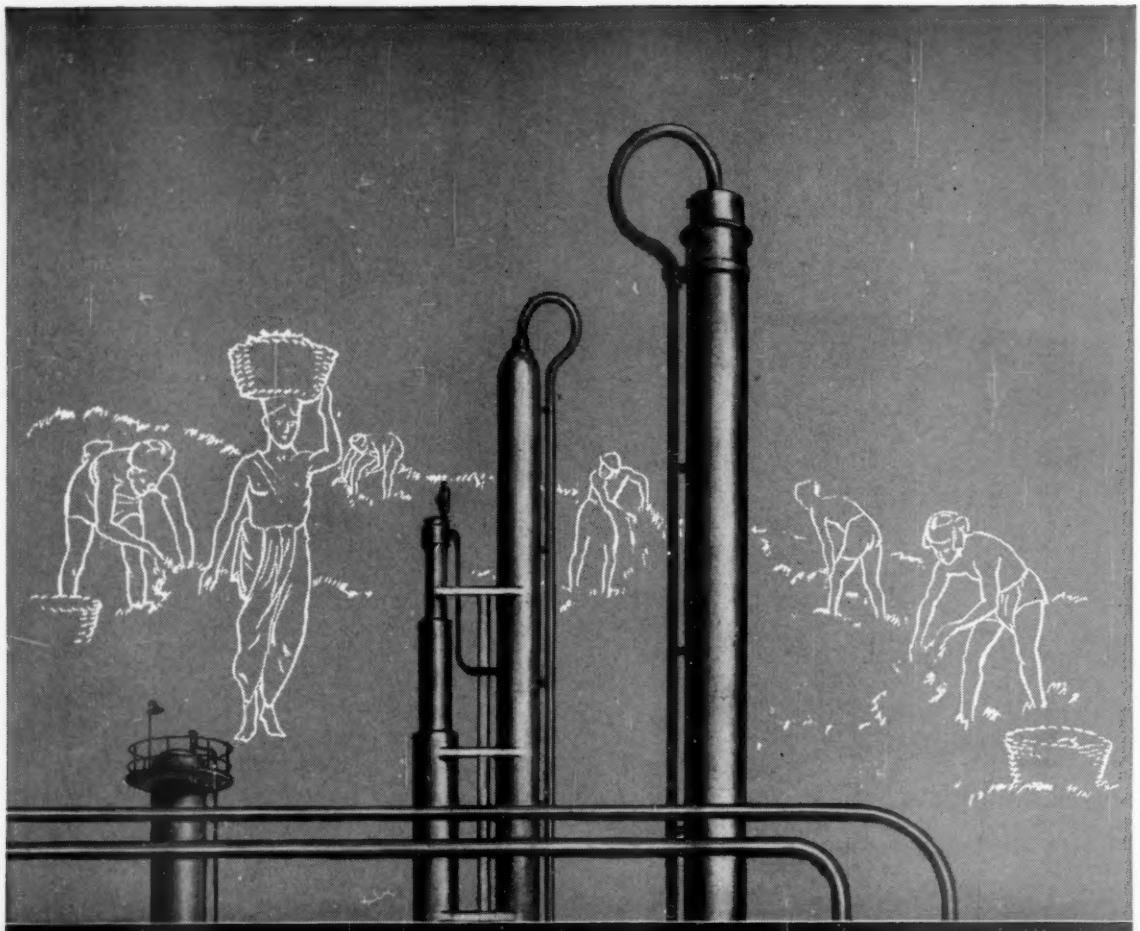
Supplied: Bottles of 50, 100 and 1000 Filmtabs

Abbott

they're POTENT

®FILMTAB—FILM-SEALED TABLETS, ABBOTT, PAT. APPLIED FOR.

706169



THE ALKALOID COMPLEX WITH LESS SIDE-EFFECTS

...yet the total therapeutic activity of RAUWOLFIA

Rautensin provides all the essential antihypertensive alkaloids

Rautensin (the alseroxylon fraction complex of Rauwolfia) contains both rescinnamine and reserpine, together with the other valuable alkaloids.

Produces a gradual and sustained drop in blood pressure.

Calms and soothes the patient without loss of alertness.

Rautensin is less likely to produce mental depression

The alseroxylon fraction complex of Rauwolfia was found less prone to cause mental depression.[1]

Does not usually cause drowsiness.

Is purified and is therefore free of inert dross present in the whole root.

1. Moyer, J.H.; Dennis, E., and Ford, R.: A.M.A. Arch. Int. Med. 96: 530, 1955

Rautensin®

Each tablet contains 2 mg. *purified* Rauwolfia serpentina alkaloids (alseroxylon fraction)

SMITH-DORSEY • Lincoln, Nebraska • a division of The Wander Company

anti-inflammatory.... bactericidal

'CORTISPORIN'®

For infected, or potentially infected, inflammatory conditions of the eye (anterior segment), ear and skin

VIRTUALLY NON-SENSITIZING

'CORTISPORIN' brand OINTMENT

Each Gm. contains: 'Aerosporin'® Sulfate Polymyxin B Sulfate 5,000 Units; Bacitracin 400 Units; Neomycin Sulfate 5 mg.; Hydrocortisone (free alcohol) 10 mg. (1%).

Available in applicator tip tubes of ⅛ oz. and ½ oz.

'CORTISPORIN' brand OTIC DROPS

Each cc. contains: 'Aerosporin'® Sulfate Polymyxin B Sulfate 10,000 Units; Neomycin Sulfate 5 mg.; Hydrocortisone (free alcohol) 10 mg. (1%).

Available in sterile dropper bottles of 5 cc.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

SYMPTOMATIC

RELIEF... PLUS!

ACHROCIDIN*

TETRACYCLINE-ANTIHISTAMINE-ANALGESIC COMPOUND

Tablets and Syrup

ACHROCIDIN is particularly valuable in treating acute respiratory infections during epidemics or when questionable middle ear, pulmonary, nephritic, or rheumatic signs are present.

ACHROCIDIN offers early, potent therapy against such disabling complications as otitis media, sinusitis, bronchitis to which the patient may be highly vulnerable at this time.

Included in the comprehensive ACHROCIDIN formulation are the analgesic components recommended for prompt relief of common cold symptoms.

Adult dosage for ACHROCIDIN Tablets and new, caffeine-free ACHROCIDIN Syrup is two tablets or teaspoonfuls of syrup three or four times daily. Dosage for children according to weight and age.

Available on Prescription Only

Each tablet contains:

ACHROMYCIN® Tetracycline	125 mg.	Caffeine	30 mg.
Phenacetin	120 mg.	Salicylamide	150 mg.
		Chlorothen Citrate	25 mg.

Lederle

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK

*Trademark

Superficial skin complaints usually respond dramatically to TASHAN CREAM 'Roche'

Antiprurient, soothing, and healing—contains vitamins A, D, E, and *d*-Panthenol, in a cosmetically pleasing water-soluble base which fastidious patients will enjoy using. Hoffmann-La Roche Inc., Nutley, N. J.

TASHAN T. M.

advanced therapy for advancing hypertension

Apresoline®

hydrochloride

(hydralazine hydrochloride CIBA)

- to lower blood pressure
- to increase renal blood flow
- to decrease cerebral vascular tone

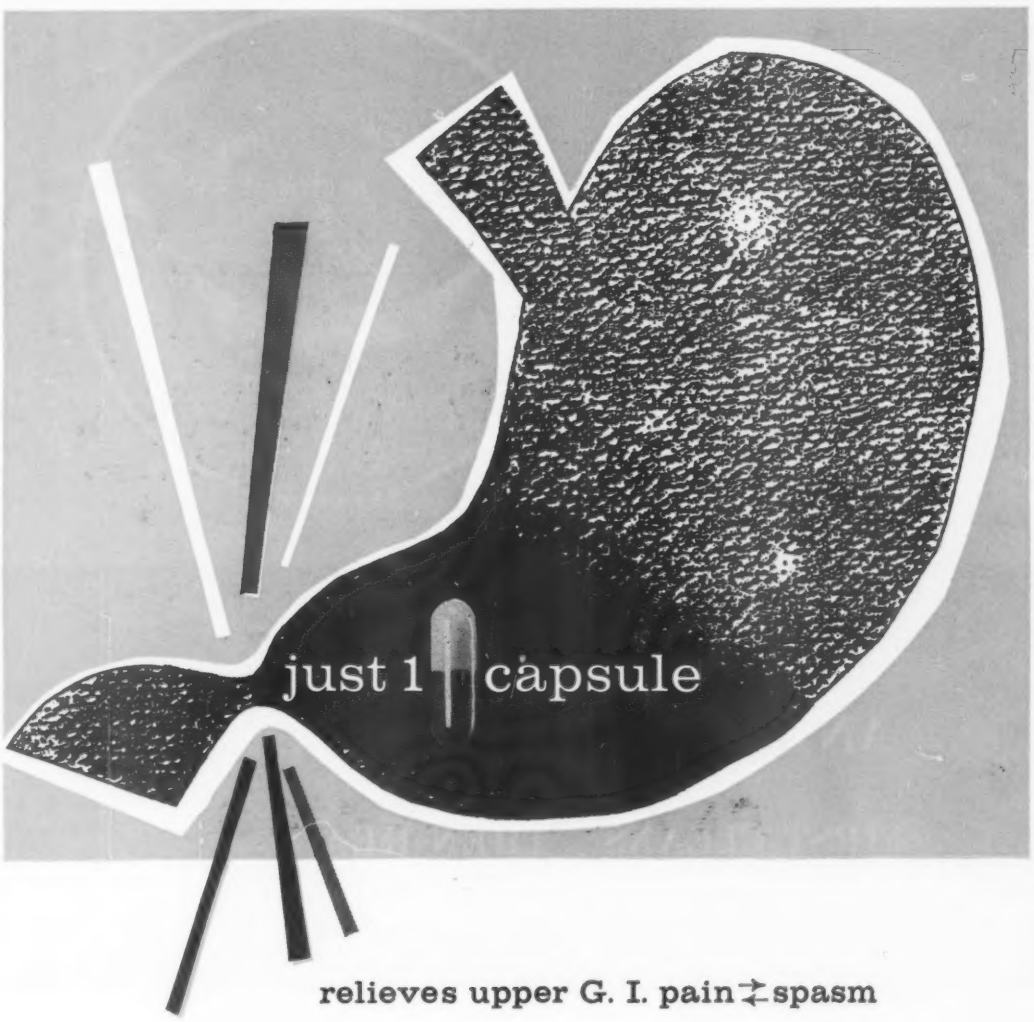
SUPPLIED: **Ampuls,** 1 ml., 20 mg. per ml.

Tablets, 10 mg. (yellow, double-scored),
25 mg. (blue, coated),
50 mg. (pink, coated);
bottles of 100, 500 and 1000.

Tablets, 100 mg. (orange, coated);
bottles of 100 and 1000.

2/2373MB

CIBA
SUMMIT, N. J.



relieves upper G. I. pain ⇄ spasm

usually in 10 minutes

visceral eutonic

DACTIL®

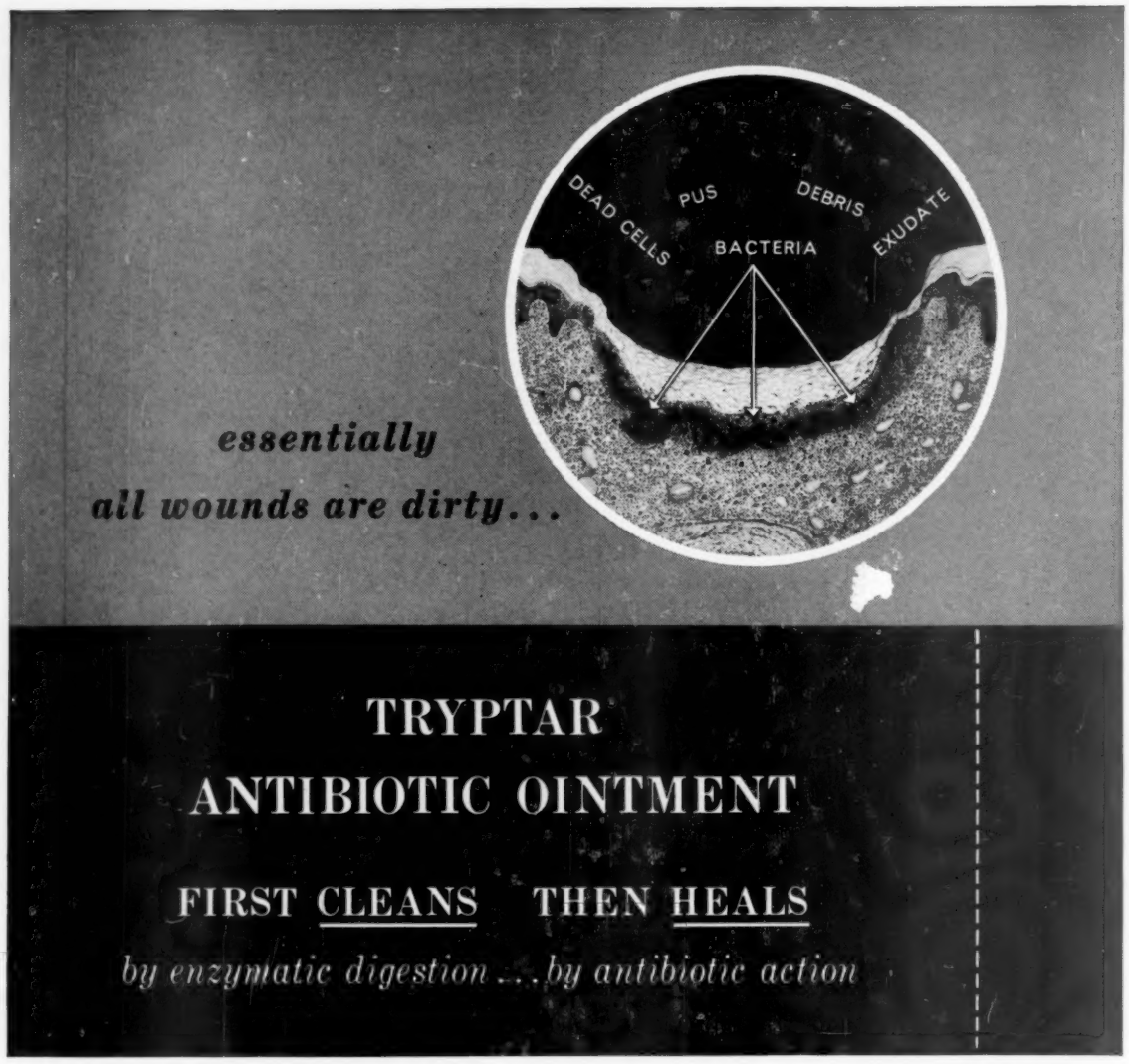
PLAIN AND WITH PHENOBARBITAL

- normalizes visceral tone and motility
- does not interfere with digestive secretions
- avoids "antispasmodic" side effects
- prescribed q.i.d. for gastroduodenal and biliary spasm, cardiospasm, pylorospasm, biliary dyskinesia, gastric neurosis and irritability

DACTIL is the *only* brand of N-ethyl-3-piperidyl diphenylacetate hydrochloride.

LAKESIDE

14157



TRYPTAR ANTIBIOTIC OINTMENT

FIRST CLEANS THEN HEALS

by enzymatic digestion ... by antibiotic action

Tryptar Antibiotic Ointment contains trypsin and chymotrypsin to clear away tissue debris, which then permits the two antibiotics, bacitracin and polymyxin, to exert full antibiotic power.

Tryptar Antibiotic Ointment can be easily applied to old, encrusted and infected wounds, as well as to fresh wounds. Its specially prepared water-soluble base facilitates removal of dirt, eschar and phagedenic membranes.

Tryptar Antibiotic Ointment may be applied as often as necessary, without fear of allergic reactions. There is no known contraindication to the use of Tryptar Antibiotic Ointment.

Each Gram of Tryptar Antibiotic Ointment Contains:

Trypsin (crystalline)	5,000 Armour Units
Chymotrypsin (crystalline)	5,000 Armour Units
Bacitracin U. S. P.	500 units
Polymyxin B Sulfate U.S.P.	5,000 units

in a specially prepared water-soluble ointment base.

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS

CLINICAL COLLOQUY

My patients complain that the pain tablets I prescribe are too slow-acting... they usually take about 30 to 40 minutes to work.

Why don't you try the new codeine derivative that's combined with APC for faster, longer-lasting pain relief?

What is it... how fast does it act?

It's Percodan®—relieves pain in *5 to 15 minutes*, with a single dose lasting 6 hours or longer.

How about side effects?

No problem. For example, the incidence of constipation with Percodan* is rare.

Sounds worth trying— what's the average adult dose?

One tablet every 6 hours. That's all.

Where can I get literature on Percodan?

Just ask your Endo detailman or write to:

Endo®

ENDO LABORATORIES

Richmond Hill 18, New York

*U. S. Pat. 2,628,185. PERCODAN contains salts of dihydrohydroxycodeinone and homatropine, plus APC. May be habit-forming. Available through all pharmacies.

"Mediatric" will help make the "senior" years more pleasant and enjoyable.

'Mediatric" is specially formulated to counteract the adverse influence of declining gonadal function, nutritional inadequacy and emotional instability.

'Mediatric" contains estrogen and androgen in amounts that will effectively supplement reduced gonadal hormone production; nutritional supplements carefully selected to meet the needs of the patient; and a mild antidepressant to promote a brighter mental outlook. Available in tablets, capsules, and liquid.

"MEDIATRIC"®

Steroid-Nutritional Compound

IN PREVENTIVE GERIATRICS

Ayerst

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

5660

Meat...

Good Nutrition and the Metabolic Changes of Adolescence

The sharp increase in nutritional requirements during adolescence is ascribed to the rapid growth, restless activity, high basal metabolism, and increased rate of organ development during this period.[1, 2] Nutrient needs during adolescence are higher than at any other period of life[3] except for pregnancy and lactation.

In order to satisfy these extremely high nutritional requirements, "protective" foods supplying liberal amounts of protein, vitamins, and minerals should predominate in adolescent diets.[3] Such foods include meat, poultry, fish, milk, eggs, vegetables and fruits, and whole-grain or enriched cereals and enriched bread. Accessory foods commonly eaten by adolescents to satisfy emotional needs may provide energy, but are commonly responsible for obesity and should not take the place of the "protective" foods.

Meat contributes much toward making the daily meals of adolescents appetizing, ample, and satisfying as well as adequate in protein, B vitamins, iron, phosphorus, potassium, and magnesium. Its complete protein functions in all physiologic mechanisms utilizing protein—tissue growth and replacement, fabrication of enzymes, hormones, and antibodies, and maintenance of the body's fluid balance. Its B vitamins and minerals take part in many processes of intermediate metabolism important in body development.

1. Toverud, K. U.; Stearns, G., and Macy, I. G.: Maternal Nutrition and Child Health. An Interpretative Review, Washington, D.C., National Research Council, National Academy of Sciences, Bull. No. 123, 1950, p. 115.
2. Proudfit, F. T., and Robinson, C. H.: Nutrition and Diet Therapy, ed. 11, New York, The Macmillan Company, 1955, p. 271.
3. Martin, E. A.: Roberts' Nutrition Work with Children, Chicago, The University of Chicago Press, 1954, pp. 231-236.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute
Main Office, Chicago... Members Throughout the United States

THE STORY OF

CARDIAC ARREST

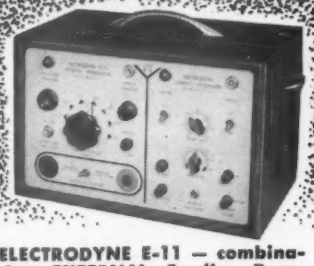
ELECTRODYNE PM-65* WITH ELECTRO-CARDIOSCOPE — detects and treats cardiac arrest automatically and externally — provides continuous visual display of electrocardiogram. (Scope optional).

ELECTRODYNE D-72 — for EXTERNALLY APPLIED treatment of ventricular fibrillation

These two important instruments are also available as one unit — Combination Pacemaker and Defibrillator. (Model 43)

ELECTRODYNE CARDIAC DEFIBRILLATOR — for emergency internal treatment of ventricular fibrillation. (Model 33)

ELECTRODYNE CARDIAC PACEMAKER — for emergency external treatment of ventricular standstill. (Model 27-A)



ELECTRODYNE E-11 — combination EXTERNAL Cardiac Pacemaker and EXTERNAL Defibrillator.

Cardiac arrest is certainly a serious occurrence in any hospital . . . that's why you should know the story about proven instruments for the detection and treatment of cardiac arrest and fibrillation.

From the introduction of the original and well known Cardiac Pacemaker, which was developed in conjunction with PAUL M. ZOLL, M.D., the Electrodyne Company has worked very closely with Dr. Zoll and his associates in continuous research and development in this specialized field of instrumentation.

Collectively these proven Electrodyne instruments represent an important family of life-saving medical equipment that is giving a feeling of security and peace of mind in the operating rooms and in the wards of hospitals throughout the world.

We will gladly send you complete literature upon request.

***The need for continuous human observation is not required when the Electrodyne PM-65 is used in the detection and treatment of cardiac arrest.**

SPECIALISTS IN

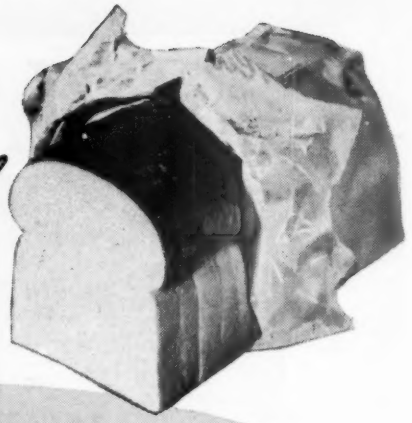
ELECTRODYNE

MEDICAL ELECTRONICS

ELECTRODYNE CO., INC.

90 ENDICOTT STREET, NORWOOD, MASSACHUSETTS

The Well-Balanced Nutrients in Enriched Bread



Equally Important in REDUCING Diets

The maintenance of an optimal nutritional state in the face of a sharp curtailment of caloric intake makes it mandatory that the daily diet satisfy all requirements for protein, vitamins, and minerals. Thus all foods present in normal diets, including meat, poultry, fish, eggs, dairy products, vegetables, fruits, and enriched and whole grain products, may be represented in the reducing diet.

The enrichment nutrients of enriched bread are selected qualitatively and quantitatively because of their importance in everyday nutrition. These nutrients have proved especially important in restricted diets.

Though relatively low in calories (only 63 per slice), enriched bread contributes noteworthy amounts of biologically valuable protein, the B vitamins thiamine, riboflavin and niacin, the minerals iron and calcium.

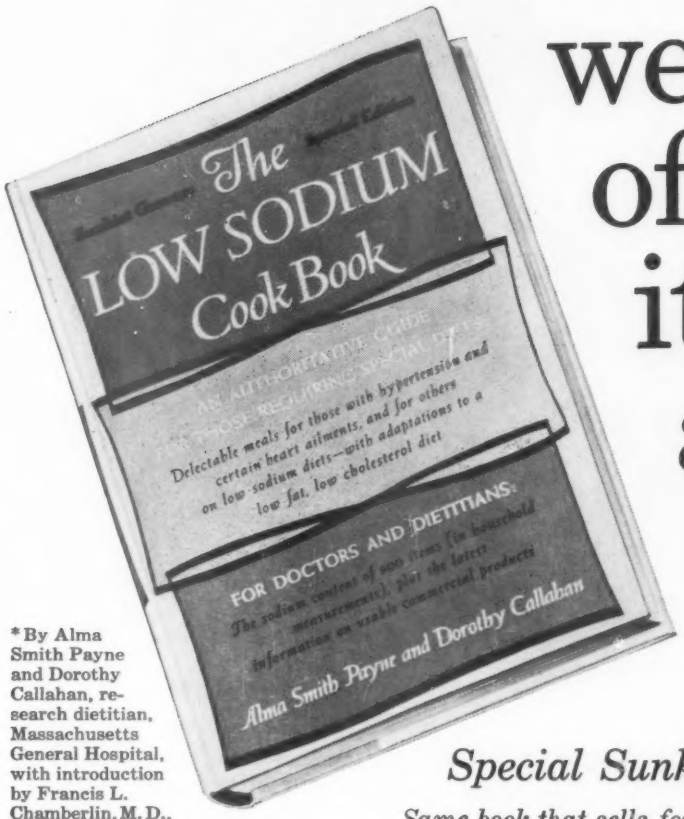
The average contribution per slice—protein 2 Gm.; thiamine 0.06 mg.; riboflavin 0.04 mg.; niacin 0.56 mg.; iron 0.6 mg.; calcium 21 mg.—merits the inclusion of enriched bread in the reducing diet, and—through the number of slices included—helps in assuring adequate intake of these essentials.

Fresh or toasted, or in sandwiches, enriched bread affords eating satisfaction so essential for making any reducing regimen tolerable over the long term usually required.

AMERICAN BAKERS ASSOCIATION
20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

so in demand—



we offer it again!

*By Alma Smith Payne and Dorothy Callahan, research dietitian, Massachusetts General Hospital, with introduction by Francis L. Chamberlin, M. D., M. Sc. D.

Special Sunkist Edition $1.25

Same book that sells for $4, except for paper cover and an added *section on fresh lemons.*

Famous Cook Book* for Low Sodium Patients. Nearly 500 pages of useful information:

- **tables of sodium, cholesterol, fat contents of 900 items in household measurements.**
- **how to follow doctor's instructions.**
- **how to accommodate the family to the diet.**
- **cooking with wines, herbs and seasonings.**
- **how to prepare meats, chicken, fish, vegtables, sauces, salads and salad dressings for the low sodium dieter.**
- **how to bake breads and desserts with low sodium substitutes.**
- **use of home freezer for the dieter.**
- **how to pack a low sodium lunch box.**
- **how to "eat out" on the diet.**

Doctors tell us lemons — as a seasoning substitute for salt—help solve the vexing problem of keeping low sodium patients on their diets by making unsalted food interesting.

You and your patients are invited to write for copies of this complete and authoritative guide to tasty low-salt menus while the limited supply lasts.

Free diet booklet, "Salt or No Salt." Please use coupon, specify quantity. You need not order The Low Sodium Cook Book to get these booklets for distribution to low sodium patients.

Sunkist ® FRESH LEMONS

SUNKIST GROWERS
Section 10306, Terminal Annex
Los Angeles 54, California

Please send me postpaid_____copies of The Low Sodium Cook Book. I enclose $_____. (Send $1.25 for each copy. Sorry, no C.O.D.'s. Send money with order. Postage prepaid in U.S. and Canada only.)

Please send me free_____copies of handy diet booklet. (No Cook Book order required.)

Name_____

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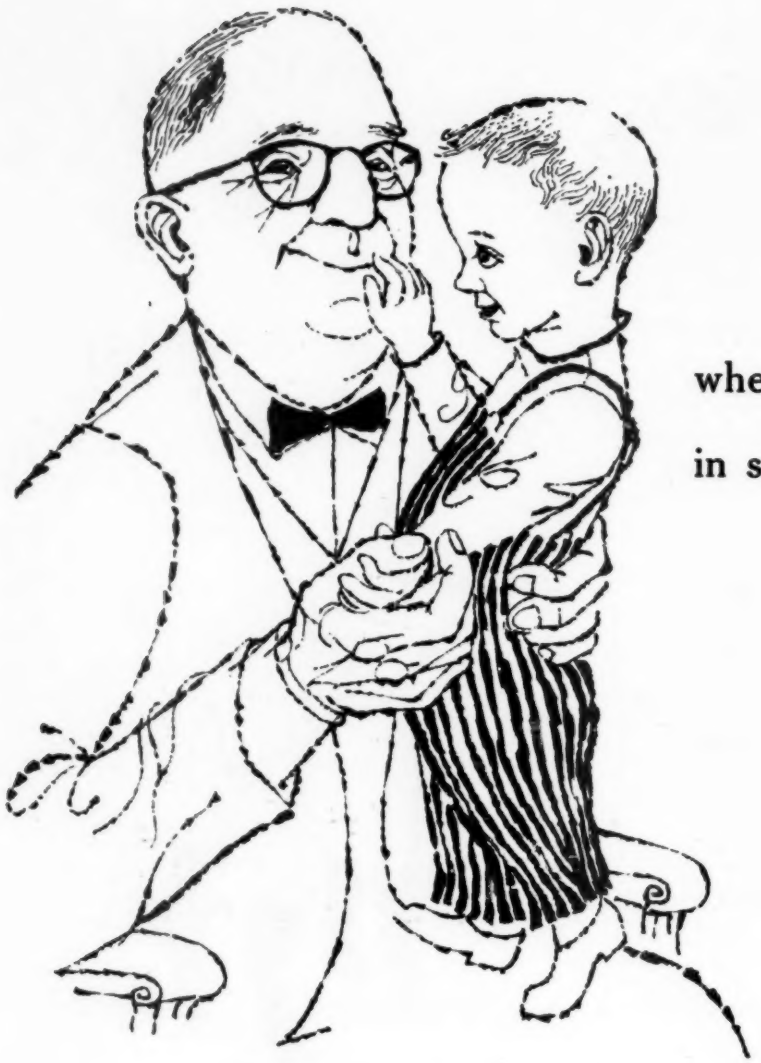

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in sedation...

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to serve every need
in barbiturate therapy

For children as well as older patients, Nembutal Elixir combines potency with the gentle action that is often so important in sedation. Like other forms of short-acting Nembutal, the elixir offers:

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- *well-tolerated* sedation . . . smaller doses . . . usually about half those of many other barbiturates
- *mild* sedation . . . hangover is rare, since the drug is swiftly and completely destroyed in the body.

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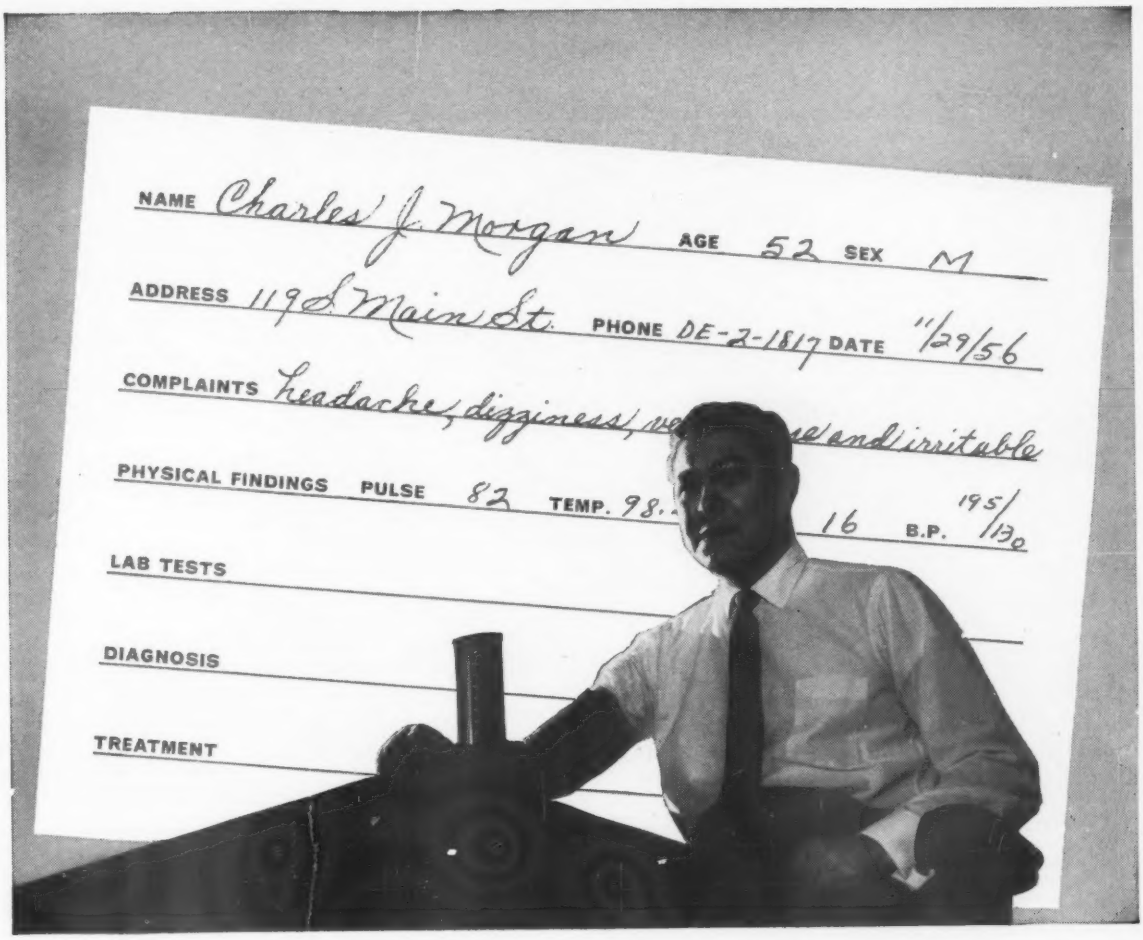

Here is Effective Antihypertensive therapy WITH GREATER SAFETY

full effects with smaller doses

Alseroxylon and alkavervir combined are much more effective than either drug used alone.[1] The resulting additive if not synergistic action[2] provides full antihypertensive effects with relatively smaller doses[3] of each component drug and with fewer side actions.

Each scored tablet of Rauvera contains 1 mg. alseroxylon and 3 mg. alkavervir.

safe initial and routine therapy

Safety is a distinguishing feature of *Rauvera*, a potent antihypertensive agent with safeguards inherent in the purified mixed alkaloid fractions, alseroxylon and alkavervir. The risks of depression,[4] postural hypotension or a reduction of blood pressure to undesirable levels are virtually absent with *Rauvera*. Patients can be started routinely on *Rauvera*. Therapy can be continued over long periods of time.

1. LaBarbera, J.F.: Med.Rec. & Ann. *50*:242, 1956. 2. Ledbetter, P.V., and Morrow, E.J.: J. Am. Geriatrics Soc. *3*:172 (March) 1955. 3. Wilkins, R.W.: Am. J. Med. *17*:703 (Nov.) 1954. 4. Moyer, J.H.; Dennis, E., and Ford, R.: A.M.A. Arch. Int. Med. *96*:530, 1955.

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24 steps to a hospital bed

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Usual Dosage: A continuous schedule of 10 to 20 mg. *before meals* and at bedtime.

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(brand of pentaerythritol tetranitrate)

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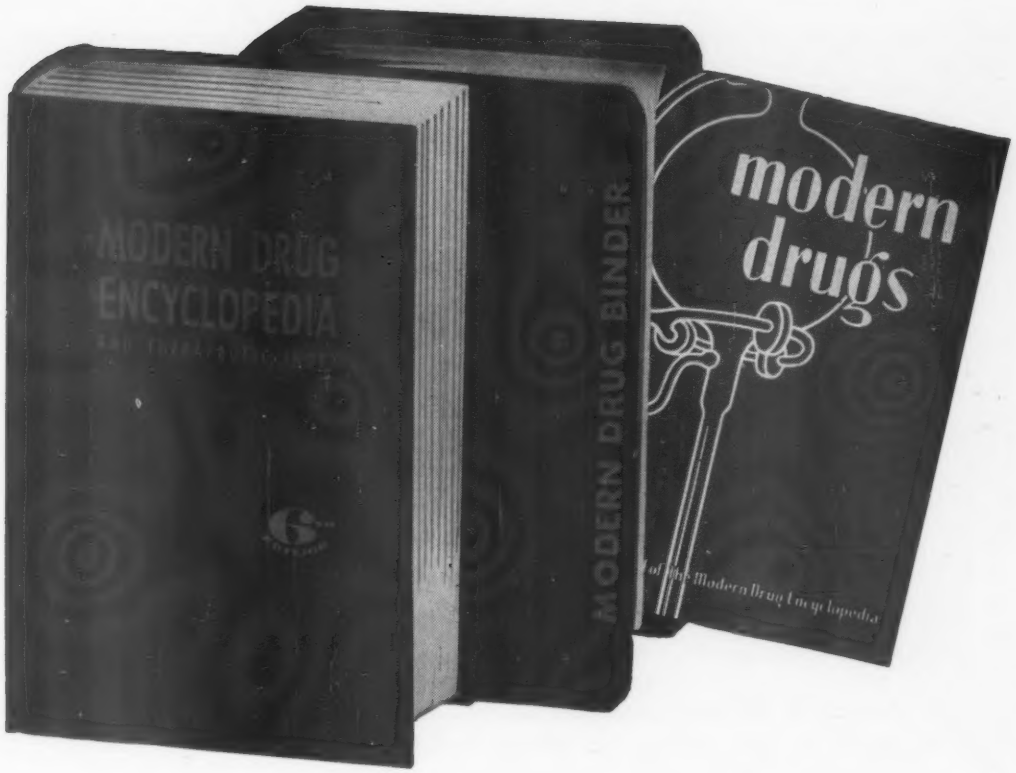

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Keyes, B. L.: Pennsylvania M. J. 60:177, Feb. 1957.

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Sokoloff, O. J.: A.M.A. Arch. Dermat. & Syph. 74:393, Oct. 1956.

4 "It ['Miltown'] ... does not cloud the sensorium, and has a helpful somnifacient effect devoid of 'hangover'."

Kessler, L. N. and Barnard, R. D.: M. Times 84:431, April 1956.

5 "In anxiety and tension states, meprobamate relaxes without dulling cortical function to the same extent as the commonly-used barbiturates."

Rindskopf, W., Ravreby, M., Gutenkauf, C. and Sands, S. L.: J. Iowa M. Soc. 47:57, Feb. 1957.

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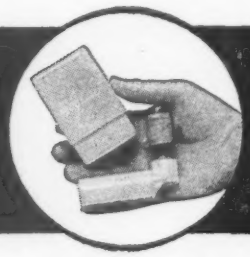

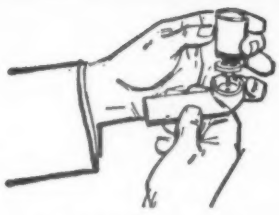

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